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Antimicrobial Activity of Cefoperazone-Sulbactam Tested against Gram-Negative Organisms from Europe, Asia-Pacific, and Latin America in 2015–2016

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Introduction

- Cefoperazone is a broad-spectrum third-generation cephalosporin with activity against gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa*
- Cefoperazone pharmacologic properties include a long elimination half-life of approximately 2 hours, which allows for twice-daily administration
- Cefoperazone was widely used in the 1980s to treat infections in neutropenic patients and immunocompetent individuals
- Because of its lability to ß-lactamases, cefoperazone was combined with the ß-lactamase inhibitor sulbactam; this combination has been used in many geographic regions to treat infections, including nosocomial pneumonia, intra-abdominal infections, gynaecological infections, sepsis, and infections in febrile neutropenic patients
- We evaluated the antimicrobial activities of cefoperazone-sulbactam tested against a large collection of clinical isolates of gram-negative organisms

Materials and Methods

Organism collection

- A total of 19,545 organisms, including 14,417 Enterobacteriaceae, 3,818 *Pseudomonas aeruginosa*, and 1,310 *Acinetobacter* spp., were collected from medical centres located in Western Europe (W-EUR; n=10,626; 26 centres in 10 nations), Eastern Europe (E-EUR; n=4,029; 15 centres in 11 nations), the Asia-Pacific region (APAC; n=2,491; 18 centres in 9 nations), and Latin America (LATAM; n=2,399; 17 centres in 11 nations) in 2015–2016 as part of the SENTRY Antimicrobial Surveillance Program
- Species identification was performed by the participating centre and confirmed at JMI Laboratories (North Liberty, Iowa, USA) when necessary by Vitek 2 or MALDI–TOF MS using the Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) by following manufacturer instructions

Susceptibility testing

- Isolates were tested for susceptibility to multiple antimicrobial agents at a central reference laboratory (JMI Laboratories) by reference broth microdilution methods as described by the CLSI M07 document (2018) using MIC panels prepared at JMI Laboratories
- Cefoperazone-sulbactam was tested at a 1:1 ratio and MIC breakpoints were those found in the Sulperazon® package insert and the Cefobid® package insert (≤16 mg/L for susceptible and ≥64 mg/L for resistance)
- MIC results were interpreted according to CLSI criteria in M100 (2018) and EUCAST breakpoint tables (2018)

Results

- Overall, 91.6% of Enterobacteriaceae were susceptible (≤16 mg/L; Sulperazon Package Insert) to cefoperazone-sulbactam ($MIC_{50/90}$, 0.5/16 mg/L), with susceptibility rates ranging from 82.0% (E-EUR) to 94.4% (W-EUR; Table 1 and Figure 1)
- Among Enterobacteriaceae from all regions combined, 85.4%/81.1% of isolates were susceptible (CLSI/EUCAST) to piperacillin-tazobactam, 90.5%/95.6% to imipenem, and 72.1%/72.1% to ceftriaxone; with some regional variation (Table 1)
- Extended-spectrum ß-lactamase (ESBL)-phenotype rates (CLSI criteria) among *E. coli*/*K. pneumoniae* were 18.4%/34.2% in W-EUR, 38.2%/72.4% in E-EUR, 26.3%/25.1% in APAC, and 34.7%/51.8% in LATAM (Table 2)
- Overall, 97.2%/77.0% of *Escherichia coli*/*Klebsiella pneumoniae* were cefoperazone-sulbactam-susceptible, including 99.5/99.4% of non-ESBL-phenotype and 90.1/50.0% of ESBL-phenotype isolates (data not shown)
- Among *P. aeruginosa* isolates, cefoperazone-sulbactam susceptibility rates were highest in APAC (84.6%), followed by W-EUR (83.0%), LATAM (83.0%), and E-EUR (59.5%; Table 3 and Figure 2)
- *P. aeruginosa* susceptibility rates for piperacillin-tazobactam, imipenem, and ceftazidime were 78.3%, 76.2%, and 82.0% in W-EUR; 52.3%, 43.5%, and 57.4% in E-EUR; 83.5%, 80.1%, and 84.5% in APAC; and 81.5%, 72.8%, and 83.0% in LATAM, respectively (Table 3)
- *Acinetobacter* spp. susceptibility rates varied from 43.0% in E-EUR to 75.8% in LATAM (53.2% overall) for cefoperazone-sulbactam and from 19.8% in E-EUR to 40.2% in W-EUR (26.4% overall) for imipenem (Table 4 and Figure 3)

Table 1 Antimicrobial activity of cefoperazone-sulbactam and comparator agents tested against Enterobacteriaceae isolates stratified by geographic region

Antimicrobial agent	% susceptible (CLSI/EUCAST)[a]				
	W-EUR (8,440)	E-EUR (2,543)	APAC (1,645)	LATAM (1,789)	All (14,417)
Cefoperazone-sulbactam[b]	94.4/-[c]	82.0/-	94.2/-	89.5/-	91.6/-
Piperacillin-tazobactam	88.8/85.1	72.5/66.8	89.8/86.5	83.7/78.0	85.4/81.1
Ampicillin-sulbactam	43.5/43.5	27.3/27.3	45.0/45.0	33.4/33.4	39.5/39.5
Amikacin	98.2/96.9	94.1/90.5	99.0/97.3	96.4/93.0	97.4/95.3
Aztreonam	82.8/80.4	56.8/53.6	81.6/78.2	66.1/63.7	76.0/73.3
Cefepime	85.7/83.9	57.7/55.4	83.2/81.8	67.5/65.8	78.2/76.4
Ceftazidime	84.3/80.3	58.3/53.9	82.0/78.5	68.4/64.1	77.5/73.4
Ceftriaxone	79.4/79.4	51.5/51.5	76.8/76.8	62.3/62.3	72.1/72.1
Ciprofloxacin	77.3/73.8	55.1/49.4	78.3/73.4	60.3/54.2	71.4/67.0
Colistin	-/82.6	-/84.0	/ 85.8	-/81.3	-/83.0
Gentamicin	89.8/89.4	70.1/69.6	86.0/85.6	73.6/72.5	83.9/83.4
Imipenem	90.7/96.3	86.7/93.1	94.3/97.4	91.0/94.5	90.5/95.6
Levofloxacin	79.6/75.4	59.8/54.0	80.5/76.4	65.9/58.8	74.5/69.7
Meropenem	97.6/97.8	91.5/92.8	97.6/97.7	94.5/95.0	96.1/96.5
Tigecycline[d]	98.0/92.7	97.8/91.6	99.0/95.2	98.3/93.0	98.1/92.8
Tobramycin	87.3/84.9	63.7/60.5	85.4/81.7	69.4/65.5	80.7/77.8
TMP-SMX	72.0/72.0	52.6/52.6	72.4/72.4	54.7/54.7	66.5/66.5

[a] Criteria as published by CLSI 2018 and EUCAST 2018.
[b] Sulperazon Package Insert (2009).
[c] -, no breakpoint has been established.
[d] US FDA/EUCAST breakpoints.
Abbreviations: W-EUR, Western Europe; E-EUR, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 2 Frequency of *E. coli* and *K. pneumoniae* isolates with an ESBL phenotype stratified by geographic region

Organism	% of isolates with ESBL phenotype (CLSI)			
	W-EUR	E-EUR	APAC	LATAM
E. coli	18.4	38.2	26.3	34.7
K. pneumoniae	34.2	72.4	25.1	51.8

Abbreviations: ESBL, extended-spectrum ß-lactamase; W-EUR, Western Europe; E-EUR, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America.

Table 3 Antimicrobial activity of cefoperazone-sulbactam and comparator agents tested against *Pseudomonas aeruginosa* isolates stratified by geographic region

Antimicrobial agent	% susceptible (CLSI/EUCAST)[a]				
	W-EUR (1,838)	E-EUR (891)	APAC (636)	LATAM (453)	All (3,818)
Cefoperazone-sulbactam[b]	83.0/-[c]	59.5/-	84.6/-	83.0/-	77.8/-
Piperacillin-tazobactam	78.3/78.3	52.3/52.3	83.5/83.5	81.5/81.5	73.5/73.5
Amikacin	93.7/89.4	66.5/61.0	94.7/92.3	87.9/84.1	86.8/82.6
Cefepime	85.4/85.4	60.5/60.5	88.2/88.2	83.0/83.0	79.8/79.8
Ceftazidime	82.0/82.0	57.4/57.4	84.5/84.5	83.0/83.0	76.8/76.8
Ciprofloxacin	78.5/75.5	52.7/47.6	85.7/82.7	78.1/75.7	73.7/70.2
Colistin	99.9/99.9	99.3/99.3	99.7/99.7	99.8/99.8	99.7/99.7
Gentamicin	84.8/84.8	56.2/56.2	91.4/91.4	81.2/81.2	78.8/78.8
Imipenem	76.2/80.1	43.5/48.5	80.1/82.4	72.8/75.5	68.8/72.6
Levofloxacin	76.8/69.3	49.3/41.3	84.0/76.8	76.1/67.9	71.5/63.9
Meropenem	78.9/78.9	46.1/46.1	82.6/82.6	74.8/74.8	71.4/71.4
Tobramycin	88.5/88.5	61.7/61.7	94.0/94.0	84.1/84.1	82.7/82.7

[a] Criteria as published by CLSI 2018 and EUCAST 2018.
[b] Sulperazon Package Insert (2009).
[c] -, no breakpoint has been established.
Abbreviations: W-EUR, Western Europe; E-EUR, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America.

Figure 1 Antimicrobial activity of cefoperazone-sulbactam against Enterobacteriaceae isolates stratified by geographic regions

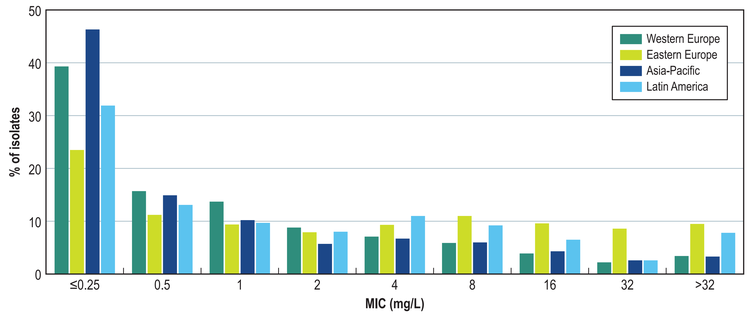

Figure 2 Antimicrobial activity of cefoperazone-sulbactam against *P. aeruginosa* isolates stratified by geographic regions

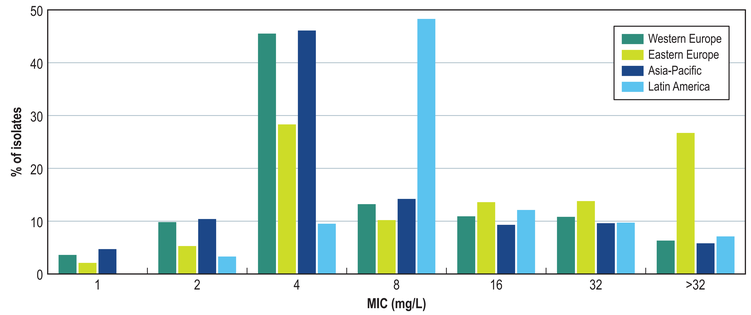

Figure 3 Antimicrobial activity of cefoperazone-sulbactam against *Acinetobacter* spp. isolates stratified by geographic regions

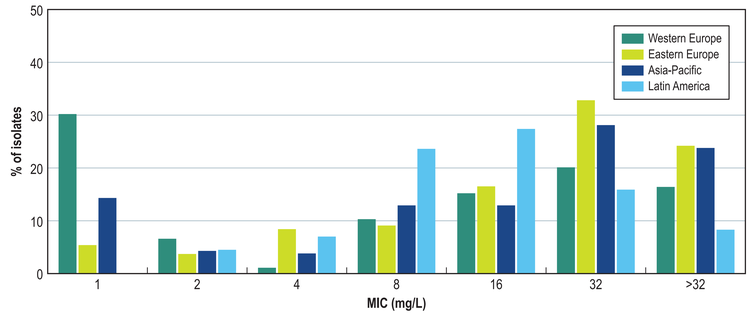

Table 4 Antimicrobial activity of cefoperazone-sulbactam and comparator agents tested against *Acinetobacter* spp. stratified by geographic region

Antimicrobial agent	% susceptible (CLSI/EUCAST)[a]				
	W-EUR (348)	E-EUR (595)	APAC (210)	LATAM (157)	All (1,310)
Cefoperazone-sulbactam[b]	63.5/-[c]	43.0/-	48.1/-	75.8/-	53.2/-
Piperacillin-tazobactam	35.9/-	7.2/-	19.0/-	17.2/-	17.9/-
Ampicillin-sulbactam	37.6/-	16.5/-	22.9/-	23.1/-	23.9/-
Amikacin	46.6/45.1	16.8/14.5	33.8/31.9	36.3/27.4	29.8/26.9
Cefepime	37.1/-	9.9/-	17.1/-	20.6/-	19.6/-
Ceftazidime	36.2/-	8.7/-	22.4/-	22.3/-	19.8/-
Ciprofloxacin	37.5/37.5	7.6/7.6	21.9/21.9	19.1/19.1	19.2/19.2
Colistin	82.1/82.1	90.7/90.7	91.9/91.9	96.2/96.2	89.3/89.3
Gentamicin	43.1/43.1	19.0/19.0	31.0/31.0	32.5/32.5	28.9/28.9
Imipenem	40.2/40.2	19.8/19.8	25.2/25.2	22.3/22.3	26.4/26.4
Levofloxacin	38.5/37.4	9.1/7.6	24.8/22.4	20.4/19.7	20.8/19.3
Meropenem	40.2/40.2	17.3/17.3	24.3/24.3	21.7/21.7	25.0/25.0
Tobramycin	44.8/44.8	40.3/40.3	35.2/35.2	50.6/50.6	41.9/41.9

[a] Criteria as published by CLSI 2018 and EUCAST 2018.
[b] Sulperazon Package Insert (2009).
[c] -, no breakpoint has been established.
Abbreviations: W-EUR, Western Europe; E-EUR, Eastern Europe and Mediterranean region; APAC, Asia-Pacific region; LATAM, Latin America.

Conclusions

- Antimicrobial susceptibility rates varied widely among geographic regions and were generally lowest in E-EUR when compared to the other geographic regions evaluated
- Cefoperazone-sulbactam continues to demonstrate *in vitro* activity against clinically important gram-negative organisms isolated from W-EUR, E-EUR, APAC, and LATAM medical centres
- Based on the potency and activity spectrum, cefoperazone-sulbactam continues to have a role for treating infections caused by gram-negative organisms and remains among the most active compounds *in vitro* against Enterobacteriaceae, *P. aeruginosa*, and *Acinetobacter* spp. at published breakpoints

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