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Antimicrobial Activities of Cefepime and Piperacillin/Tazobactam against *E. coli* and *Klebsiella* spp. with ESBL-phenotype Collected Worldwide

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SENTRY ANTIMICROBIAL SURVEILLANCE

AMENDED ABSTRACT

Background: Cefepime (CPM) exhibits more stability to hydrolysis by ESBLs compared to other cephalosporins and piperacillin/tazobactam (P/T) may be active against these pathogens due to the inhibitory activity of tazobactam. These compounds may represent a reasonable option to treat infections caused by ESBL-producing strains.

Methods: 50,637 clinical isolates (34,367 *E. coli* [EC] and 16,270 *Klebsiella* spp. [KSP]) were collected from > 80 medical centers during the 1998-2004 period and tested for susceptibility (S) by CLSI broth microdilution methods. Isolates with an ESBL-phenotype (MIC ≥ 2 µg/ml for aztreonam or ceftazidime or ceftriaxone) were submitted to a clavulanate inhibitory test (disk approximation and/or Etest) for confirmation of ESBL production.

Results: Among isolates from North America (NA), 3.9% of EC and 8.6% of KSP showed an ESBL phenotype, while among isolates from the rest of the world (ROW; Europe, Latin America and Asia) 7.7% of EC and 28.3% showed this phenotype. Confirmation rates varied from 21 (NA) to 39% (ROW) for EC and from 50 (NA) to 53% (ROW) among KSP. The activities of CPM and P/T is summarized in the table.

	MIC_{50} (µg/ml)/% S			
	CPM		P/T	
Organism (no. NA/ROW)	NA	ROW	NA	ROW
ESBL-Phenotype				
EC (556/1,554)	0.25/90.3	4/62.2	8/82.7	8/74.3
KSP (643/2,485)	1/89.4	8/60.2	32/48.9	32/42.8
ESBL-Confirmed				
EC (120/603)	4/65.8	16/42.0	8/72.5	8/69.1
KSP (322/1,313)	2/89.4	8/51.2	16/52.6	32/45.0
ESBL-Not-confirmed				
EC (436/951)	0.25/97.0	1/75.1	4/85.5	8/77.5
KSP (321/1,172)	0.5/89.4	4/70.4	32/45.1	64/40.3

CPM was generally more active than P/T, while isolates from NA showed higher rates of S to both drugs compared to isolates from ROW. ESBL not confirmed strains showed generally higher S rates than ESBL-confirmed strains.

Conclusions: ESBL production was not confirmed in a large proportion of EC (61-79%) and KSP (47-50%) isolates with an ESBL phenotype. CPM showed acceptable activity against isolates with an ESBL phenotype isolated in NA.

INTRODUCTION

The emergence and broad dissemination of extended-spectrum ß-lactamase (ESBL)-producing strains has presented a great threat to the use of many classes of antimicrobial agents, particularly cephalosporins. Although no randomized trials have been performed on evaluating treatment of infections due to ESBL-producing organisms, it has been well recognized that poor outcome occurs when patients with serious infections with such organisms are treated with antimicrobial agents to which the organism is frankly resistant. However, the mortality rate is significantly lower when patients are treated with antimicrobials with MIC values in the susceptible range.

In the majority of reports in which clinical failure was attributed to "inappropriate" therapy, ceftazidime was used to treat infections caused by an ESBL-producing organism for which MIC values for ceftazidime were very high, often > 32 µg/ml. Thus, controversy exists as to whether cephalosporin therapy is appropriate for ESBL-producing organisms for which cephalosporin MIC values are in the susceptible range, a scenario that could be relatively common.

In the present study, we evaluated the in vitro activity of cefepime, piperacillin/tazobactam and selected antimicrobial agents against ESBL-producing strains collected through the SENTRY Antimicrobial Surveillance Program worldwide.

MATERIALS AND METHODS

The SENTRY Program has monitored the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals in 4 major geographic regions: Asia-Pacific, Europe, Latin America, and the United States/Canada. We report here the antimicrobial susceptibility patterns of ESBL-producing *Escherichia coli* and *Klebsiella* spp. collected in the 1998-2004 period. The isolates were divided in two groups, those collected in North American medical centers and those collected in all other regions monitored by the program (Rest Of World [ROW]).

Individual, non-duplicate strains were consecutively collected (prevalence format by infection site) from bloodstream, respiratory tract, urinary tract and skin/soft tissue infections. All isolates were identified by the participant laboratories and confirmed by the monitoring facility (JMI Laboratories, North Liberty, Iowa). Each strain was tested by a reference broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) methods and interpretive criteria. Concurrent quality control testing was performed using the following organisms: *E. coli* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213 and *Klebsiella pneumoniae* 700603. All QC results were within published ranges.

A total of 50,637 clinical isolates (34,367 *E. coli* and 16,270 *Klebsiella* spp.) were collected during the study period (1998-2004). Isolates with increased MIC values (≥ 2 µg/ml) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as ESBL-phenotype and submitted to a clavulanate inhibition test (disk approximation and/or Etest [AB BIODISK, Solna, Sweden]) for confirmation of ESBL production. The antimicrobial susceptibility patterns of ESBL-confirmed strains (ESBL-phenotype and a positive confirmation test result) were compared to that of ESBL-not-confirmed strains (ESBL-phenotype and a negative confirmation test result).

RESULTS

- The prevalence of *E. coli* with an ESBL-phenotype was lower in North America (3.9%) compared to the ROW (7.7%). In addition, ESBL-production was confirmed in only 21.6% of the North American isolates compared to 38.8% of the ROW isolates (Table 1).
- The prevalence of *Klebsiella* spp. with an ESBL-phenotype was also lower in North America (8.6%) compared to the ROW (28.3%). However, confirmation rates were similar in both geographic areas, e.g. 50.1% in North America and 52.8% in the ROW (Table 1).
- In general, only 45.0% (2,358 of 5,238) of isolates with an ESBL-phenotype had the ESBL production confirmed (Table 1).
- Cefepime was highly active against *E. coli* strains with an ESBL-phenotype collected in North America (90.3% susceptibility), especially against ESBL-not-confirmed strains (MIC_{90}, 2 µg/ml; 97.0% susceptibility). *E. coli* with an ESBL-phenotype isolated in the ROW showed higher resistance rates to cefepime and most antimicrobials evaluated when compared to North American isolates (Tables 2 and 3).
- Cefepime also showed reasonable activity against *Klebsiella* spp. strains with an ESBL-phenotype collected in North America (MIC_{90}, 16 µg/ml; 89.4% susceptibility). Piperacillin/tazobactam was active against only 48.9% of the isolates at the current CLSI susceptible breakpoint, and susceptibility rates were also low for other antimicrobials, such as gentamicin (46.0%) and ciprofloxacin (56.5%; Table 2).
- *Klebsiella* spp. strains with an ESBL-phenotype isolated in the ROW showed low rates of susceptibility to all antimicrobials tested, except imipenem (99.5% susceptibility; Table 3).

Table 1. Prevalence of ESBL-phenotype and ESBL-producing (confirmed) strains.

	% Prevalence of:		
Organism (no. tested)[a]	ESBL-phenotype	ESBL-confirmed	ESBL-not-confirmed
E. coli			
NA (14,127)	3.9	0.8	3.1
ROW (20,240)	7.7	3.0	4.7
Klebsiella spp.			
NA (7,487)	8.6	4.3	4.3
ROW (8,783)	28.3	15.0	13.3

a. NA = North America (USA and Canada) and ROW = Rest Of World.

Table 2. Antimicrobial susceptibility of strains with ESBL-phenotype from North America.

	% susceptible		
Organism (no. tested) /antimicrobial agent	ESBL-phenotype	ESBL-confirmed	ESBL-not-confirmed
E. coli	(556)	(120)	(436)
Cefepime	90.3	65.8	97.0
Piperacillin/tazobactam	82.7	72.5	85.5
Ceftazidime	57.0	36.7	62.6
Ceftriaxone	67.1	39.2	74.8
Aztreonam	66.4	35.0	75.0
Cefoxitin	31.1	46.0	27.0
Imipenem	100.0	100.0	100.0
Gentamicin	69.8	50.0	75.2
Ciprofloxacin	61.9	29.2	70.9
Klebsiella spp.	(643)	(322)	(321)
Cefepime	89.4	89.4	89.4
Piperacillin/tazobactam	48.9	52.6	45.1
Ceftazidime	35.8	19.3	52.3
Ceftriaxone	53.2	37.9	68.3
Aztreonam	34.7	16.1	53.3
Cefoxitin	48.3	55.8	40.0
Imipenem	97.0	99.7	94.4
Gentamicin	46.0	30.4	61.7
Ciprofloxacin	56.5	50.6	62.3

Table 3. Antimicrobial susceptibility of strains with ESBL-phenotype from Europe, Latin America, Asia and Australia.

	% susceptible		
Organism (no. tested) /antimicrobial agent	ESBL-phenotype	ESBL-confirmed[a]	ESBL-not-confirmed
E. coli	(1,554)	(603)	(951)
Cefepime	62.2	42.0	75.1
Piperacillin/tazobactam	74.3	69.1	77.5
Ceftazidime	53.7	38.5	63.3
Ceftriaxone	39.1	18.1	52.4
Aztreonam	41.6	22.6	53.6
Cefoxitin	47.1	61.7	37.9
Imipenem	99.9	100.0	99.8
Gentamicin	52.6	46.1	56.8
Ciprofloxacin	41.8	37.6	44.5
Klebsiella spp.	(2,485)	(1,313)	(1,172)
Cefepime	60.2	51.2	70.4
Piperacillin/tazobactam	42.8	45.0	40.3
Ceftazidime	32.5	29.2	36.2
Ceftriaxone	23.4	17.0	30.6
Aztreonam	20.2	15.2	25.8
Cefoxitin	69.3	75.0	62.9
Imipenem	99.5	99.8	99.1
Gentamicin	38.6	32.2	45.7
Ciprofloxacin	67.8	69.8	65.4

a. Based on the disk approximation test.

CONCLUSIONS

- The prevalence of Enterobacteriaceae isolates evaluated in this seven year study with a CLSI ESBL-phenotype were not ESBL-producers.
- *E. coli* and *Klebsiella* spp. strains with an ESBL-phenotype isolated in North America showed higher antimicrobial susceptibility rates compared to those isolated in the ROW.
- In general, cefepime showed higher activity than piperacillin/tazobactam against *E. coli* and *Klebsiella* spp. strains with an ESBL-phenotype. Cefepime was particularly active against ESBL-not-confirmed *E. coli* strains.

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