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Potency and Antimicrobial Spectrum Update for Piperacillin/Tazobactam (2000): Emphasis on its Activity Against Resistant Organism Populations and Generally Untested Species Causing Community-Acquired Respiratory Tract Infections

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ABSTRACT

The in vitro activity of piperacillin/tazobactam and several comparison broad-spectrum compounds was assessed against recent clinical isolates of Gram-positive and -negative bacteria from geographically diverse medical centers in Europe, North and Latin America participating in various surveillance programs in 2000. Several organisms were characterized for phenotypic expression of various resistant determinants such as extended-spectrum ß-lactamase (ESBL) or amp C cephalosporinase hyperproduction, and vancomycin resistance in enterococci (VRE). Piperacillin/tazobactam retained activity (MIC_{90}) against oxacillin-susceptible *Staphylococcus* spp. (0.12 - 0.5 µg/ml), *Bacillus* spp. (0.5 µg/ml), vancomycin-susceptible enterococci (> 4 µg/ml), and *Corynebacterium* spp. (2 µg/ml; not including *C. jeikeium*) with susceptibility rates of 100.0, 91.7, 85.7 and 81.8%, respectively. Piperacillin/tazobactam inhibited all *Streptococcus* spp. strains at ≤ 16 µg/ml, including penicillin-resistant strains many of which were co-resistant to erythromycin (90%) and other ß-lactams. A specific breakpoint for these streptococci when testing piperacillin/tazobactam appears needed to prevent false-resistant reports using penicillin as a class representative. The carbapenems among ß-lactams were the most active agents against the ESBL-producing species of *Escherichia coli* and *Klebsiella pneumoniae* and those strains which hyper-express amp C enzymes including *Citrobacter* spp. and *Enterobacter* spp. Piperacillin/tazobactam only exhibited modest activity against the "amp C resistance group" strains (68.8% susceptible or intermediate, MIC ≤ 64 µg/ml). Piperacillin/tazobactam (MIC_{50}, 8 µg/ml; 79.5% susceptible) was the most active agent tested against multi-drug resistant isolates of *Pseudomonas aeruginosa*. Against sampled *Haemophilus influenzae* (39.2% ampicillin-resistant), piperacillin/tazobactam (MIC_{90}, ≤ 0.06 µg/ml), ceftriaxone and ceftazidime inhibited 100.0% of the isolates at ≤ 0.25 µg/ml. These in vitro surveillance results from the year 2000 on three continents, demonstrated a sustained potent activity of piperacillin/tazobactam against selected problematic nosocomial and community-acquired pathogens. The potential importance of these findings is that this ß-lactamase inhibitor combination can be used an empiric treatment of serious infections in hospital environments where resistance has emerged, as well as covering nearly all isolates of fastidious respiratory tract pathogens acquired in the community setting.

INTRODUCTION

Over the past decade, the rapid emergence and spread of antimicrobial resistance among several clinically significant nosocomial and community-acquired pathogens has seen the genesis of many surveillance studies to monitor these trends and to provide valuable information to guide empiric treatment of these infections. Among the most common species causing community-acquired respiratory tract infections (CARTI), *Haemophilus influenzae* ampicillin-resistant rates of 33 to 34% and *Streptococcus pneumoniae* penicillin-resistant rates of 14% in the United States (1997-99) have recently been reported. Additionally, with enteric bacilli being associated with 30% of nosocomial infections, the increasing rates of amp C cephalosporinase or extended-spectrum ß-lactamase (ESBLs) mediated resistances has raised concern among many clinicians.

Due to the proliferation of various resistance mechanisms, the efficacy of ß-lactam antimicrobials has been compromised. However, by combining ß-lactamase inhibitors (clavulanic acid, sulbactam, tazobactam) with older penicillins (ticarcillin, ampicillin, piperacillin), a strong synergistic effect provides a dramatically expanded spectrum of activity against many species of Gram-negative and -positive aerobic and anaerobic organisms that may harbor these resistance mechanisms.

In this study, the in vitro activity of piperacillin/tazobactam against Gram-positive and -negative organisms including selected resistant species such as vancomycin-resistant enterococci, ß-lactamase producing Enterobacteriaceae, and prominent CARTI organisms was compared to several antimicrobials representing different classes of compounds.

MATERIALS AND METHODS

A total 797 selected bacterial strains were tested and consisted of the following species: *H. influenzae* (97 strains), oxacillin-susceptible *S. aureus* (51 strains), oxacillin-susceptible coagulase-negative staphylococci (CoNS; 16 strains), *S. pneumoniae* (114 strains), ß-haemolytic streptococci (99 strains), viridans group streptococci (108 strains), *Enterococcus* spp. (56 strains; 50% vancomycin-resistant), *Corynebacterium jeikeium* (eight strains), other *Corynebacterium* spp. (11 strains), *Bacillus* spp. (12 strains), *Citrobacter* spp and *Enterobacter* spp. (93 strains with amp C-mediated resistance), *Pseudomonas aeruginosa* (39 strains), ESBL-producing *Escherichia coli* (32 strains) or *Klebsiella pneumoniae* (61 strains). Isolates were collected from more than 60 medical centers in Europe, North America and Latin America participating in surveillance trials in 2000 and 2001. Strain identification was determined using accepted, conventional laboratory tests and the identifications and/or phenotypic confirmations were performed at a reference laboratory (JMI Laboratories, North Liberty, Iowa, USA).

MICs were determined by the reference broth microdilution method according to procedures recommended by the National Committee for Clinical Laboratory Standards (NCCLS) [NCCLS, 2000]. Mueller-Hinton broth with 3-5% lysed horse blood was used for testing common *Streptococcus* spp., and Haemophilus Test Medium (HTM) was used for testing the *H. influenzae* strains. Reference trays were incubated in ambient air at 35ºC for 18-24 hours. Quality control (QC) was monitored using the following organisms: *S. pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212, *H. influenzae* ATCC 49247, and *E. coli* ATCC 25922. All QC results were within published control limits [NCCLS, 2002]. Interpretations of susceptibility categories were established from NCCLS [2002] tables.

RESULTS

- Piperacillin/tazobactam and imipenem (100% susceptibile) were the only tested agents with activity against all of the oxacillin-susceptible strains of *S. aureus*. (Table 1).
- Piperacillin/tazobactam (MIC_{90}, ≤0.5 µg/ml) was second to imipenem (MIC_{90}, ≤0.06 µg/ml) and two- to 16-fold more active than ciprofloxacin and ceftazidime in potency against oxacillin-susceptible CoNS. (Table 1).
- Against vancomycin-susceptible enterococci, piperacillin/tazobactam activity (85.7% susceptible) was equal to ampicillin and surpassed only by chloramphenicol (92.9-100.0% susceptible). (Table 1).
- Only chloramphenicol and quinupristin/dalfopristin (92.9 and 71.4% susceptible, respectively) were active against vancomycin-resistant enterococci. (Table 1).
- Piperacillin/tazobactam activity (MIC_{90}, 0.25 µg/ml, 100% susceptible) against ß-haemolytic streptococci was superior to erythromycin, clindamycin and chloramphenicol and compared favorably to penicillin (0.06 µg/ml; 100%), amoxicillin (0.25 µg/ml; 100%), ceftriaxone (≤0.25 µg/ml; 100%), imipenem (≤0.06 µg/ml; 100%) and levofloxacin (1 µg/ml; 100%). (Table 1).
- Levofloxacin (95.7% susceptible) was slightly more active than clindamycin and ceftriaxone (91.7% susceptible) against viridans group streptococci. (Table 1).
- Piperacillin/tazobactam had good activity against *Bacillus* spp. and *Corynebacterium* spp. (91.7 and 81.8% susceptible, respectively), but not *C. jeikeium* (87.5% resistant). (Table 1).

Table 1. Activity of piperacillin/tazobactam and selected comparison agents tested against recent clinical isolates of Gram-positive species.

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category:[a] Susceptible	Resistant
S. aureus (51)[b]	Piperacillin/Tazobactam	0.5	2	0.12-2	100.0	0.0
	Ceftazidime	8	8	4-16	98.0	0.0
	Imipenem	≤0.06	≤0.06	≤0.06-0.5	100.0	0.0
	Gentamicin	≤1	≤1	≤1->8	98.0	2.0
	Ciprofloxacin	≤0.25	0.5	≤0.25->2	94.1	5.9
	Quinupristin/Dalfopristin	0.25	0.25	≤0.06->2	98.0	0.0
CoNS (16)[c]	Piperacillin/Tazobactam	0.12	0.5	≤0.06-1	100.0	0.0
	Ceftazidime	4	8	1-16	93.8	0.0
	Imipenem	≤0.06	≤0.06	≤0.06	100.0	0.0
	Gentamicin	≤1	≤1	≤1	100.0	0.0
	Ciprofloxacin	≤0.25	1	≤0.25->2	93.8	6.2
	Quinupristin/Dalfopristin	0.25	0.25	0.12-0.25	100.0	0.0
Enterococci vancomycin-susceptible (28)	Piperacillin/Tazobactam	4	>128	1->128	85.7[d]	14.3
	Ampicillin	2	>16	≤0.12->16	85.7	14.3
	Imipenem	2	>8	≤0.06->8	-[e]	-
	Ciprofloxacin	2	>2	≤0.25->2	46.4	46.4
	Quinupristin/Dalfopristin	8	>8	0.25->8	21.4	71.4
	Chloramphenicol	8	8	1->16	92.9	7.1
vancomycin-resistant (28)	Piperacillin/Tazobactam	>128	>128	2->128	21.4[d]	78.6
	Ampicillin	>16	>16	1->16	21.4	78.6
	Imipenem	>8	>8	2->8	-	-
	Ciprofloxacin	>2	>2	0.5->2	3.6	96.4
	Quinupristin/Dalfopristin	1	>8	0.25->8	71.4	25.0
	Chloramphenicol	8	8	4->16	92.9	7.1
ß-haem. streptococci (99)	Piperacillin/Tazobactam	≤0.06	0.25	≤0.06-0.25	100.0[f]	-
	Penicillin	≤0.015	0.06	≤0.015-0.12 100.0	0.0	-
	Amoxicillin	≤0.06	0.25	≤0.06-0.25	100.0[f]	0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0	0.0
	Imipenem	≤0.06	≤0.06	≤0.06	100.0[f]	0.0
	Levofloxacin	0.5	1	≤0.5-2	100.0	0.0
	Erythromycin	≤0.25	>8	≤0.25->8	83.8	15.2
viridans gr. streptococci (108)	Piperacillin/Tazobactam	0.25	8	≤0.06-16	47.2[f]	-
	Penicillin	0.25	8	≤0.015->16	47.2	25.9
	Amoxicillin/Clavulanate	≤2	>8	2->8	47.2[f]	25.9
	Ceftriaxone	≤0.25	2	≤0.25-8	91.7	4.6
	Imipenem	≤0.06	0.25	≤0.06-4	47.2[f]	25.9
	Levofloxacin	1	2	≤0.5->4	95.7	4.3
	Erythromycin	≤0.25	4	≤0.25->8	51.9	41.7
	Clindamycin	≤0.06	0.12	≤0.06->8	91.7	8.3
Bacillus spp. (12)	Piperacillin/Tazobactam	0.5	1	≤0.06-32	91.7	0.0
Corynebacterium spp. (11)	Piperacillin/Tazobactam	2	32	≤0.06->128	81.8	9.1
C. jeikeium (8)	Piperacillin/Tazobactam	>128	-	16->128	12.5	87.5

a. Susceptibility criteria of the NCCLS [2002] or as indicated in parentheses, if not available in NCCLS documents.
b. All strains are oxacillin-susceptible (MIC, ≤2 µg/ml).
c. Oxacillin-susceptible only (MIC, ≤0.25 µg/ml).
d. A total of 85.7% of strains were inhibited at ≤16 µg/ml e.g. equal to ampicillin and amoxicillin/clavulanate.
e. - = no criteria listed in NCCLS [2002] tables.
f. Susceptibility predicted by the penicillin results.

- Piperacillin/tazobactam inhibited all *S. pneumoniae* (including penicillin-intermediate and -resistant) at ≤8 µg/ml including levofloxacin-resistant strains. (Table 2).

Table 2. Distribution of piperacillin/tazobactam MIC results from 114 strains of *S. pneumoniae* from blood cultures categorized by susceptibility to penicillin. Six comparison agents are also listed.

Penicillin susceptibility (no. tested)	Antimicrobial agent	% of strains at each MIC (µg/ml) ≤0.06	0.12	0.25	0.5	1	2	4	8	>	Susceptible breakpoint (µg/ml)	C_{max}/route[a]
Susceptible (44)	Piperacillin/Tazobactam	98	0	0	2	0	0	0	0	0	-[b]	242/IV
	Amoxicillin/Clavulanate	-[c]	-	100	0	0	0[d]	0	0	0	≤2	11/PO
	Ceftriaxone	100	0	0	0	0	0	0	0	0	≤1	151/IV
	Ceftazidime	-	-	80	9	7	4	0	0	0	-	69/IV
	Erythromycin	-	-	83	0	0	5	5	5	2	≤0.25	1-2/PO
	Levofloxacin	0	2	0	29	59	0	5	-	5	≤2	6/PO
Intermediate (35)	Piperacillin/Tazobactam	6	3	14	23	28	23	3	0	0	-[b]	242/IV
	Amoxicillin/Clavulanate	-	-	43	14	29	14	0	0	0	≤2	11/PO
	Ceftriaxone	7	20	33	26	7	0	7	0	0	≤1	151/IV
	Ceftazidime	-	-	3	9	11	14	43	17	3	-	69/IV
	Erythromycin	-	-	49	3	9	9	9	0	21	≤0.25	1-2/PO
	Levofloxacin	0	0	0	35	51	0	0	-	14	≤2	6/PO
Resistant (35)	Piperacillin/Tazobactam	0	0	0	0	0	23	74	3	0	-[b]	242/IV
	Amoxicillin/Clavulanate	-	-	0	0	22	53	9	13	3	≤2	11/PO
	Ceftriaxone	0	0	0	13	77	0	10	0	0	≤1	151/IV
	Ceftazidime	-	-	0	0	0	0	0	60	40	-	69/IV
	Erythromycin	-	-	11	0	9	31	17	0	32	≤0.25	1-2/PO
	Levofloxacin	3	3	0	0	29	48	0	-	17	≤2	6/PO

a. Maximum serum drug concentration in µg/ml following usual dosing route found in the product package insert.
b. No interpretive criteria are listed in the NCCLS tables [2002].
c. - = untested concentration.
d. Underlined value is at the susceptible breakpoint [NCCLS, 2002].

- Piperacillin/tazobactam (MIC_{90}, ≤0.06 µg/ml) activity against *H. influenzae* (39% ampicillin-resistant) was superior to amoxicillin/clavulanate and cefuroxime and equivalent to ceftriaxone.(Table 3).

Table 3. Distribution of piperacillin/tazobactam MIC results for 97 recent clinical isolates of *H. influenzae* isolated from patients with pneumonia compared to five other broad-spectrum ß-lactams or ß-lactamase inhibitor combinations.

Antimicrobial agent	% of strains at each MIC (µg/ml) ≤0.06	0.12	0.25	0.5	1	2	4	>	Susc. breakpoint (µg/ml)
Piperacillin/Tazobactam	97	2	1	0	0	0	0	0	≤1
Amoxicillin/Clavulanate	-[a]	-	37	32	20	11	0	0	≤4
Ampicillin[b]	-	-	-	55	6	1	2	36	≤1
Cefuroxime	0	1	5	36	36	14	8	0	≤4
Ceftriaxone	100	0	0	0	0	0	0	0	≤2

a. - = untested concentrations
b. A total of 60.8% of strains were susceptible to ampicillin (ß-lactamase-negative).

- Piperacillin/tazobactam activity against selected resistant populations of enteric bacilli was limited: *Citrobacter* and *Enterobacter* spp., Amp C resistant (MIC_{90}, >64 µg/ml), ESBL-positive *E. coli* and *K. pneumoniae* (MIC_{90}, >128 µg/ml). (Table 4).
- Piperacillin/tazobactam was the most active agent tested against *P. aeruginosa* (79.5% susceptible) although one-third of the isolates were multiple-drug resistant phenotypes. (Table 4).

Table 4. Activity of piperacillin/tazobactam and selected broad-spectrum agents tested against selected resistant populations of Gram-negative species.

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category: Susceptible	Resistant
Citrobacter spp. and *Enterobacter* spp. amp C resistant group (93)[a]	Piperacillin/Tazobactam	64	>64	2->64	26.9	31.2
	Imipenem	0.5	1	0.12-8	98.9	0.0
	Meropenem	≤0.06	0.25	≤0.06-4	100.0	0.0
	Gentamicin	≤1	>8	≤1->8	72.0	28.0
	Tobramycin	1	>16	0.25->16	58.1	41.9
	Amikacin	2	16	0.5->32	90.3	9.7
	Ciprofloxacin	≤0.25	>2	≤0.25->2	66.7	30.1
	Trim/Sulfa	≤0.5	>2	≤0.5->2	58.1	35.5
E. coli (ESBL-positive; 32)[b]	Piperacillin/Tazobactam	128	>128	1->128	34.4	56.2
	Ceftriaxone	>32	>32	2->32	12.5	71.9
	Ceftazidime	16	>16	1->16	46.9	31.3
	Cefepime	16	>16	0.25->16	40.6	46.9
	Imipenem	0.12	0.5	≤0.06-0.5	100.0	0.0
	Meropenem	≤0.06	0.12	≤0.06-0.12	100.0	0.0
	Tobramycin	>16	>16	0.5->16	25.0	75.0
	Ciprofloxacin	≤0.25	>2	≤0.25->2	50.0	50.0
K. pneumoniae (ESBL-positive; 61)[b]	Piperacillin/Tazobactam	>128	>128	4->128	19.7	68.9
	Ceftriaxone	>32	>32	≤0.25->32	18.0	52.5
	Ceftazidime	>16	>16	2->16	21.3	73.8
	Cefepime	8	>16	0.25->16	57.4	29.5
	Imipenem	0.25	0.5	≤0.06-2	100.0	0.0
	Meropenem	≤0.06	0.12	≤0.06-2	100.0	0.0
	Tobramycin	>16	>16	0.25->16	16.4	78.7
	Ciprofloxacin	≤0.25	>2	≤0.25->2	80.3	16.4
P. aeruginosa (39)	Piperacillin/Tazobactam	8	128	0.5->128	79.5	20.5
	Piperacillin	16	>128	≤0.5->128	69.2	30.8
	Ticarcillin/Clavulanate	64	>128	8->128	56.4	43.6
	Ceftazidime	4	>16	1->16	64.1	28.2
	Imipenem	1	>8	0.5->8	64.1	25.6
	Meropenem	1	>8	≤0.6->8	74.4	23.1
	Tobramycin	1	>16	≤0.12->16	74.4	25.6
	Ciprofloxacin	0.5	>2	≤0.25->2	59.0	38.5

a. Ceftazidime MIC at ≥32 µg/ml indicating a stably derepressed amp C resistance mechanism.
b. MICs for ceftriaxone and/or ceftazidime and/or aztreonam at ≥2 µg/ml.

CONCLUSIONS

- Piperacillin/tazobactam continues to demonstrate broad activity against contemporary, clinical pathogens, which include: oxacillin-susceptible *S. aureus*, oxacillin-susceptible CoNS, vancomycin-susceptible enterococci, ß-haemolytic streptococci, viridans gr. streptococci, penicillin-resistant *S. pneumoniae*, *H. influenzae* and *P. aeruginosa*.

- Piperacillin/tazobactam demonstrates value in its continued spectrum as an alternative treatment in the empiric therapy of patients with serious infections.