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Comparative Activity of Broad-Spectrum Antimicrobial Agents Used in the Treatment of Serious Infections Caused by Non-Enteric Gram Negative Bacilli: Seventh Year Report from the MYSTIC Program (USA; 1999-2005)

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

ABSTRACT

Background: The MYSTIC Program is a longitudinal surveillance network of >100 medical centers worldwide that monitors the activity of broad-spectrum agents used for serious invasive infections. In the USA, 15 centers submit 200 clinical isolates from defined organism groups each year deemed responsible for significant clinical disease.

Methods: From 1999-2005, a total of 3,913 non-Enteric Gram-negative bacilli (20.7%) were submitted to a central reference laboratory and susceptibility (S) tested using CLSI broth microdilution methods and interpretive criteria (2006). Identifications of organisms were confirmed using standard biochemical tests and the Vitek system, as required. Strains were isolated from respiratory tract (40.9%), skin and skin structure (18.9%), blood (12.7%) and intra-abdominal infections (1.0%) among others.

Results: Against *P. aeruginosa* (PSA) isolates (72.5%), MEM demonstrated a 2-fold greater potency (MIC$_{50}$ 0.5 µg/ml) compared to IMP resulting in increased S rates (87.8 vs. 85.1%, see table). MEM was more potent (2- to 4-fold lower MIC$_{50}$) against *Alcaligenes* spp. (ALC), *Burkholderia* spp. (BUC), and *Aeromonas* spp. (AERO) groups with a 3.2-25.0% higher S rate. *Acinetobacter* spp. (ASP) and *Pseudomonas* spp. non-*aeruginosa* (PSP) had a 2-fold lower IMP MIC$_{50}$ than MEM and displayed 5.1-5.7% higher S rates.

Organism (no. tested)	Agent	MIC$_{50}$	MIC$_{90}$	Range	%S[a]	%R[a]
PSA (2843)	MEM	0.5	8	≤0.016->32	87.8	7.5
	IMP	1	8	0.03->32	85.1	8.8
ASP (614)	MEM	0.5	16	≤0.016->32	81.9	13.5
	IMP	0.25	8	≤0.016->32	87.0	7.0
ALC (150)	MEM	0.25	4	≤0.016->32	92.0	5.3
	IMP	1	8	0.06->32	88.7	4.0
PSP (141)	MEM	1	8	≤0.016->32	78.7	9.9
	IMP	0.5	8	0.06->32	84.4	7.1
BUC (48)	MEM	2	8	≤0.016-32	77.1	6.3
	IMP	4	32	0.12->32	52.1	27.1
AERO (32)	MEM	0.25	1	≤0.016-16	93.8	6.3
	IMP	1	4	0.06-16	90.6	6.3

a. CLSI M100-S16 breakpoints applied.

Conclusions: These updated MYSTIC Program results show the consistently greater potency and spectrum of MEM compared to IMP against PSA, ALC, BUC, and AERO, and slightly reduced activity (2-fold compared to IMP) was observed for the ASP and PSP groups. MEM continues to display wide coverage of current pathogens expressing the most problematic resistance phenotypes.

INTRODUCTION

Non-Enterobacteriaceae Gram-negative bacilli frequently cause nosocomially acquired serious infections such as bacteremia and pneumonia which are often multidrug-resistant (MDR) including to aminoglycosides, cephalosporins, and fluoroquinolones. The carbapenems have remained one of the most active antimicrobial classes for the treatment of these infections, but resistance has increased significantly in recent years. Several mechanisms currently observed in Gram-negative bacilli confer resistance to the carbapenems, including 1) hyper-production of AmpC ß-lactamase, 2) loss of outer membrane proteins (OMPs), 3) over-expression of efflux pumps, 4) production of metallo-ß-lactamases (MßL; IMP, VIM, SPM, etc.) and 5) production of serine carbapenemases (Bush group 2F; IMI, NmcA, KPC and SME). Metallo-ß-lactamases have remained very rare in *Pseudomonas aeruginosa* in the United States (USA), but have been observed more frequently in Europe, Asia and Latin America.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program is a global antimicrobial resistance surveillance study initiated in 1997, now monitoring more than 100 medical centers worldwide. In the USA, 10 to 15 medical centers have been monitored since 1999 with bacterial strains tested by a central laboratory design (JMI Laboratories, North Liberty, Iowa) using reference broth microdilution susceptibility testing methods according to Clinical and Laboratory Standards Institute (CLSI) guidelines. These surveillance studies facilitate the detection of resistance or dissemination of mechanisms within a local region or on a global scale, particularly in hospitals using carbapenem agents. Such studies can aid in the control and minimization of resistance spread, and thus provide valuable information to clinicians when selecting empiric therapy. We report the trends of the antimicrobial susceptibility testing results from the USA MYSTIC Program non-Enterobacteriaceae Gram-negative bacilli collected over seven years, between 1999 and 2005.

MATERIALS AND METHODS

Specimen Collection: Annually since 2000, 15 medical centers geographically dispersed across the USA have been monitored which utilize carbapenems for the treatment of serious infections. Each center was requested to submit 200 bacterial isolates collected from serious infections according to specific protocol quotas among Enterobacteriaceae, non-fermentative Gram-negative species (this report), and Gram-positive cocci. *Stenotrophomonas maltophilia* and *Enterococcus faecium* isolates were excluded due to intrinsic resistances to carbapenems. All isolates were shipped to the central laboratory (JMI Laboratories).

Between 1999 and 2005, a total of 3,913 non-Enterobacteriacae Gram-negative bacilli (Table 1) were submitted from the medical centers, including *P. aeruginosa* (2,843 strains), *Acinetobacter* spp. (614 strains), *Alcaligenes* spp. (150 strains), other *Pseudomonas* spp. non-*aeruginosa* (141 strains), *Burkholderia* spp. (48 strains), *Aeromonas* spp. (32 strains), and other non-fermentative Gram-negative bacilli (85 strains). Identification of the strains were performed locally and confirmed at the central laboratory using colonial morphology, biochemical tests (Remel, Lenexa, Kansas, USA) and/or the Vitek System identification cards (bioMerieux, Hazelwood, MO, USA), as required.

Susceptibility Testing: All antimicrobial susceptibility testing was performed using validated commercially-prepared, (TREK Diagnostics, Cleveland, OH, USA) panels for all strains using CLSI reference methods to determine MIC values for the tested antimicrobial agents. Interpretation of susceptibility and resistance was based on CLSI criteria (M100-S16). Quality control (QC) was assured utilizing appropriate American Type Culture Collection (ATCC) strains with all QC results within CLSI published ranges.

RESULTS

- Meropenem had the highest overall susceptibility rate (86.7%), against the non-Enterobacteriaceae Gram-negative bacilli tested, followed by imipenem (85.3%), tobramycin (85.3%) and piperacillin/tazobactam (84.8%; data not shown).
- Table 2 shows the potencies and susceptibility/resistance rates for all tested pathogens. When compared to imipenem, meropenem was four-fold more potent against *Alcaligenes* spp. and *Aeromonas* spp.; two-fold more potent against *P. aeruginosa* (MIC$_{50}$, 0.5 µg/ml) and *Burkholderia* spp.; but 2-fold less potent against *Acinetobacter* spp. (MIC$_{50}$, 0.5 µg/ml) and the other *Pseudomonas* spp. non-*aeruginosa* isolates.

Table 1. Distribution of non-Enteric Gram-negative bacilli collected in the USA MYSTIC Program by year (1999-2005).

Organism Group (no. tested)	1999	2000	2001	2002	2003	2004	2005
P. aeruginosa (2,843)	193	299	298	321	454	689	589
Acinetobacter spp. (614)[a]	32	56	79	69	111	142	125
Alcaligenes spp. (150)[b]	7	13	16	24	18	40	32
Other *Pseudomonas* spp. (141)[c]	3	15	15	19	22	28	39
Burkholderia spp. (48)[d]	2	9	7	5	7	6	12
Aeromonas spp. (32)[e]	3	3	1	1	1	9	14
Other non-Enteric bacilli (85)[f]	6	6	9	12	8	19	25
Total (3,913)	246	401	425	451	621	933	836

a. Includes: *Acinetobacter baumannii* (442 strains), *A. calcoaceticus* (2 strains), *A. haemolyticus* (1 strain), *A. junii* (4 strains), *A. lwoffii* (60 strains), and *Acinetobacter* species (105 strains).
b. Includes: *Alcaligenes faecalis* (31 strains), *A. xylosoxidans* (92 strains), and *Alcaligenes* species (27 strains).
c. Includes: *Pseudomonas diminuta* (1 strain), *P. fluorescens/putida* (99 strains), *P. luteola* (3 strains), *P. mendocina* (4 strains), *P. oryzihabitans* (9 strains), *P. stutzeri* (14 strains), *P. vesicularis* (1 strain), and *Pseudomonas* species (10 strains).
d. Includes: *Burkholderia cepacia* (46 strains) and *B. gladioli* (2 strains).
e. Includes: *Aeromonas caviae* (2 strains), *A. hydrophila* (18 strains), *A. veronii* (4 strains), and *Aeromonas* species (8 strains).
f. Includes: *Achromobacter xylosoxidans* (7 strains), *Agrobacterium radiobacter* (7 strains), *Bordetella bronchiseptica* (2 strains), *Chryseobacterium gleum* (2 strains), *Chryseobacterium indologenes* (2 strains), *Delftia acidovorans* (6 strains), *Eikenella corrodens* (4 strains), *Kingella kingae* (2 strains), *Myroides ordoratum* (2 strains), *Ochrobactrum anthropi* (5 strains), *Pasteurella multocida* (16 strains), *Pasteurella* spp. (4 strains), *Plesiomonas* spp. (2 strains), *Ralstonia pickettii* (4 strains), *Roseomonas* spp. (3 strains), *Sphingobacterium paucimobilis* (7 strains) and one strain each of 10 other species.

Table 2. Antimicrobial activity of meropenem and eight broad-spectrum comparator agents tested against isolates in the USA MYSTIC Program (1999-2005).

Organism/antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% by category:[a] Susceptible	Intermediate	Resistant
P. aeruginosa (2,843)						
Meropenem	0.5	8	≤0.016->32	87.8	4.7	7.5
Imipenem	1	8	0.03->32	85.1	6.1	8.8
Ceftriaxone	>32	>32	≤0.25->32	12.3	20.3	67.4
Ceftazidime	2	>16	≤0.12->16	84.3	4.4	11.3
Cefepime	4	16	≤0.12->16	84.4	9.6	6.0
Piperacillin/Tazobactam	8	128	≤1->128	89.6	-	10.4
Gentamicin	≤2	>8	≤2->8	84.9	4.9	10.2
Tobramycin	≤1	4	≤1->8	90.7	1.1	8.2
Ciprofloxacin	≤0.25	>2	≤0.25->2	73.2	5.1	21.7
Acinetobacter spp. (614)						
Meropenem	0.5	16	≤0.016->32	81.9	4.6	13.5
Imipenem	0.25	8	≤0.016->32	87.0	6.0	7.0
Ceftriaxone	16	>32	≤0.25->32	29.0	35.8	35.2
Ceftazidime	8	>16	≤0.12->16	59.8	6.7	33.6
Cefepime	8	>16	≤0.12->16	58.1	17.1	24.8
Piperacillin/Tazobactam	8	>128	≤1->128	60.9	13.4	25.7
Gentamicin	≤2	>8	≤2->8	64.7	3.9	31.4
Tobramycin	≤1	>8	≤1->8	81.4	3.7	14.8
Ciprofloxacin	≤0.25	>2	≤0.25->2	58.8	1.5	39.7
Alcaligenes spp. (150)						
Meropenem	0.25	4	≤0.016->32	92.0	2.7	5.3
Imipenem	1	8	0.06->32	88.7	7.3	4.0
Ceftriaxone	32	>32	≤0.25->32	28.7	24.6	46.7
Ceftazidime	4	16	≤0.12->16	86.0	6.7	7.3
Cefepime	16	>16	≤0.12->16	30.7	30.6	38.7
Piperacillin/Tazobactam	≤1	8	≤1->128	94.7	2.0	3.3
Gentamicin	>8	>8	≤2->8	28.7	2.6	68.7
Tobramycin	>8	>8	≤1->8	29.3	2.7	68.0
Ciprofloxacin	>2	>2	≤0.25->2	17.3	20.7	62.0
Other *Pseudomonas* spp. (141)						
Meropenem	1	8	≤0.016->32	78.7	11.4	9.9
Imipenem	0.5	8	0.06->32	84.4	8.5	7.1
Ceftriaxone	16	>32	≤0.25->32	47.5	27.7	24.8
Ceftazidime	2	16	≤0.12->16	88.7	2.8	8.5
Cefepime	2	8	≤0.12->16	90.1	6.4	3.5
Piperacillin/Tazobactam	8	32	≤1->128	85.1	9.2	5.7
Gentamicin	≤2	8	≤2->8	87.9	3.6	8.5
Tobramycin	≤1	4	≤1->8	90.8	1.4	7.8
Ciprofloxacin	≤0.25	>2	≤0.25->2	78.0	7.1	14.9
Burkholderia spp. (48)						
Meropenem	2	8	≤0.016-32	77.1	16.7	6.2
Imipenem	4	32	0.12->32	52.1	20.8	27.1
Ceftriaxone	16	>32	0.5->32	43.8	27.0	29.2
Ceftazidime	4	>16	≤0.12->16	81.3	0.0	18.7
Cefepime	8	>16	0.5->16	62.5	12.5	25.0
Piperacillin/Tazobactam	2	128	≤1->128	77.1	6.2	16.7
Gentamicin	>8	>8	≤2->8	8.3	0.0	91.7
Tobramycin	>8	>8	≤1->8	8.3	2.1	89.6
Ciprofloxacin	2	>2	≤0.25->2	37.5	12.5	50.0
Aeromonas spp. (32)						
Meropenem	0.25	1	≤0.016-16	93.8	0.0	6.2
Imipenem	1	4	0.06-16	90.6	3.2	6.2
Ceftriaxone	≤0.25	2	≤0.25-8	100.0	0.0	0.0
Ceftazidime	0.25	0.5	≤0.12-4	100.0	0.0	0.0
Cefepime	≤0.12	0.25	≤0.12-1	100.0	0.0	0.0
Piperacillin/Tazobactam	2	32	≤1-128	87.5	9.4	3.1
Gentamicin	≤2	≤2	≤2->8	96.9	0.0	3.1
Tobramycin	≤1	4	≤1-4	100.0	0.0	0.0
Ciprofloxacin	≤0.25	≤0.25	≤0.25	100.0	0.0	0.0
Other non-Enteric spp. (85)						
Meropenem	0.06	4	≤0.016->32	90.6	2.3	7.1
Imipenem	0.25	4	≤0.016->32	94.1	2.4	3.5
Ceftriaxone	1	>32	≤0.25->32	69.4	14.1	16.5
Ceftazidime	2	>16	≤0.12->16	74.1	8.3	17.6
Cefepime	2	>16	≤0.12->16	78.8	5.9	15.3
Piperacillin/Tazobactam	≤1	128	≤1->128	84.7	5.9	9.4
Gentamicin	≤2	>8	≤2->8	68.2	3.5	28.2
Tobramycin	2	>8	≤1->8	58.8	4.7	36.5
Ciprofloxacin	≤0.25	>2	≤0.25->2	82.4	4.7	12.9

a. Criteria as published by the CLSI M100-S16 (2006).

- Tobramycin demonstrated the highest overall susceptibility rate (90.7%) against *P. aeruginosa* (2,843 strains) followed by piperacillin/tazobactam (89.6%) and meropenem (87.8%). Against *Acinetobacter* spp. (614 strains), imipenem (MIC$_{90}$, 8 µg/ml; 87.0%) was the most active agent followed by meropenem (MIC$_{90}$, 16 µg/ml; 81.9%) and tobramycin (MIC$_{90}$, >8 µg/ml; 81.4%; Table 2).
- Imipenem (MIC$_{90}$, 8 µg/ml; 87.0% susceptibility) was the most active compound tested against *Acinetobacter* spp. (614 strains), followed by meropenem (MIC$_{90}$, 16 µg/ml; 81.9%) and tobramycin (MIC$_{90}$, >8 µg/ml; 81.4%). All the remaining broad-spectrum agents had susceptibility rates ≤64.7% (Table 2).
- Ceftazidime exhibited the highest overall susceptibility rate against *Burkholderia* spp. (48 strains; 81.3%, susceptibility), followed by meropenem and piperacillin/tazobactam (77.1%), cefepime (62.5%), and imipenem (52.1%; Table 2).
- Minimal change in susceptibility rates for the two carbapenems and two broad-spectrum cephalosporins tested against *P. aeruginosa*, *Acinetobacter* spp., *Alcaligenes* spp. and other *Pseudomonas* spp. non-*aeruginosa* groups was observed during the 1999-2005 period (Table 3). In contrast, *Acinetobacter* spp. resistance rates varied widely in the same period driven by local clonal outbreaks (data not shown).

Table 3. Percent susceptible and resistance rates for selected non-Enteric Gram-negative bacilli groups tested in the USA MYSTIC Program (1999-2005) indexed by year.

Organism group/ antimicrobial agent	% susceptible / resistant by year:[a] 1999	2000	2001	2002	2003	2004	2005
P. aeruginosa (no. strains)	(193)	(299)	(298)	(321)	(454)	(689)	(589)
Meropenem	78.2/16.1	84.3/10.0	85.9/8.4	93.1/4.4	88.3/7.3	90.1/6.0	87.6/6.8
Imipenem	78.2/18.7	80.9/13.4	85.6/8.7	88.5/7.5	84.6/9.5	87.8/5.1	84.4/7.3
Cefepime	79.3/7.3	81.3/9.7	84.2/5.4	87.9/5.3	85.7/6.2	82.7/5.8	86.9/4.8
Ceftazidime	82.9/10.9	82.6/13.0	85.6/10.1	85.7/9.7	83.7/10.8	82.6/13.4	86.9/9.8
Acinetobacter spp. (no. strains)	(32)	(56)	(79)	(69)	(111)	(142)	(125)
Meropenem	78.1/21.9	78.6/19.6	81.0/19.0	84.1/13.0	87.4/7.2	76.1/16.2	85.6/8.0
Imipenem	81.3/6.2	80.4/10.7	83.5/11.4	88.4/11.6	91.9/1.8	83.8/8.5	92.0/3.2
Cefepime	68.8/12.5	60.7/26.8	51.9/26.6	53.6/27.5	63.1/18.0	51.4/31.7	64.0/22.4
Ceftazidime	68.8/18.8	66.1/28.6	64.6/29.1	58.0/34.8	64.0/32.4	49.3/41.5	60.8/33.6
Alcaligenes spp. (no. strains)	(7)	(13)	(16)	(24)	(18)	(40)	(32)
Meropenem	100.0/0.0	76.9/23.1	100.0/0.0	91.7/4.2	88.9/5.6	97.5/2.5	87.5/3.1
Imipenem	57.1/0.0	61.5/23.1	93.8/0.0	87.5/4.2	83.3/5.6	97.5/0.0	96.9/0.0
Cefepime	42.9/28.6	46.2/38.5	25.0/31.2	29.2/37.5	33.3/44.4	25.0/52.5	31.3/25.0
Ceftazidime	100.0/0.0	76.9/15.4	87.5/0.0	91.7/8.3	72.2/16.7	85.0/5.0	90.6/6.3
Other *Pseudomonas* spp. (no. strains)	(3)	(15)	(15)	(19)	(22)	(28)	(39)
Meropenem	66.7/0.0	53.3/20.0	73.3/13.3	68.4/21.1	81.8/9.1	85.7/3.6	89.7/5.1
Imipenem	66.7/33.3	73.3/13.3	86.7/13.3	68.4/15.8	86.4/4.5	89.3/0.0	92.3/2.6
Cefepime	66.7/33.3	80.0/6.7	66.7/0.0	78.9/15.8	95.5/0.0	89.3/0.0	94.9/2.6
Ceftazidime	100.0/0.0	93.3/6.7	93.3/0.0	73.7/26.3	90.9/4.5	92.9/7.1	87.2/7.7

a. Criteria as published by the CLSI M100-S16 (2006).

CONCLUSIONS

- Overall, the carbapenems showed the widest activity among the broad-spectrum antimicrobial agents tested in the USA MYSTIC Program followed by tobramycin and piperacillin/tazobactam.
- Among the non-Enteric Gram-negative bacilli tested, meropenem was more potent (lower MIC$_{50s}$ and MIC$_{90s}$) and demonstrated higher susceptibility rates than imipenem against *P. aeruginosa*, *Alcaligenes* spp. *Burkholderia* spp, and *Aeromonas* spp. groups. Imipenem showed higher in vitro activity than meropenem only against *Acinetobacter* spp. and other *Pseudomonas* spp. non-*aeruginosa* groups.
- The susceptibility and resistance rates remained stable among *P. aeruginosa* and other non-Enterobacteriaceae Gram-negative bacilli in the 1999-2005 period, but clonal epidemics have been documented for some species.
- Continued surveillance is warranted to monitor the activity of the carbapenems and comparator broad-spectrum antimicrobial agents against the non-Enterobacteriaceae Gram-negative bacilli.

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SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2006). *M100-S16, Performance standards for antimicrobial susceptibility testing; sixteenth informational supplement.* Wayne, PA: CLSI.
3. Jones RN, Mendes C, Turner PJ, Masterton R (2005). An overview of the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program: 1997-2004. *Diagn Microbiol Infect Dis* 53: 247-256.
4. Masterton RG, Turner PJ (2005). Overview of the Meropenem Yearly Susceptibility Test Information Collection (1997-2004). *Diagn Microbiol Infect Dis* 53: 245-246.
5. Turner PJ (2005). Use of a program-specific website to disseminate surveillance data obtained from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Study. *Diagn Microbiol Infect Dis* 53: 273-279.
6. Unal S, Garcia-Rodriguez JA (2005). Activity of meropenem and comparators against *Pseudomonas aeruginosa* and *Acinetobacter* spp. isolated in the MYSTIC Program, 2002-2004. *Diagn Microbiol Infect Dis* 53: 265-271.