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Update on Potency and Spectrum of Activity of Meropenem and Selected Broad-Spectrum Agents: Testing Results from the USA MYSTIC Program (2006)

PR RHOMBERG, JT KIRBY, TR FRITSCHE, HS SADER, RN JONES
JMI Laboratories, North Liberty, IA, USA

Contact details:
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370
319.665.3371 fax
ronald-jones@jmilabs.com

MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

AMENDED ABSTRACT

Objectives: To monitor the potency and spectrum of meropenem (MEM) and 10 other broad-spectrum agents against pathogens collected from hospitalized patients within USA medical centers actively using carbapenems (CARBs) for the treatment of serious infections. The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program is a longitudinal resistance (R) surveillance network with >100 sites worldwide. In the USA (2006), 15 sites continued participation by submitting 200 consecutive, non-duplicate clinical isolates from defined pathogen groups.
Methods: 2,841 isolates (95% compliance) including 1,260 Enterobacteriaceae (ENT), 606 *P. aeruginosa* (PSA), 456 oxacillin-susceptible *S. aureus* (MSSA), 300 streptococci, 149 *E. faecalis*, and 70 Gram-positive anaerobes were tested using CLSI reference broth microdilution or agar dilution susceptibility (S) methods and associated interpretative criteria. Extended-spectrum beta-lactamase (ESBL) phenotype strains were confirmed using Etest methods, negative strains were then screened for acquired AmpC genes (8 classes) by PCR. Serine carbapenemase (C-ase) production was screened by disk approximation and characterized by PCR. All fluoroquinolone (FQ)-R ENT isolates were tested for a *qnr* using PCR.
Results: The CARB class had the lowest R rates against ENT (3.3–4.0%) and the FQs had the highest R rates (21.7-22.5%). MEM was the most potent agent tested with an 8-fold lower MIC_{90} compared to imipenem against ENT strains and was 2-fold more potent against PSA strains (MIC_{90}, 8 vs. 16 mg/L). Among *Klebsiella* spp. (KSP), 9.2% (57) possessed KPC-type serine C-ase from sites in New York (2), New Jersey, and Ohio at rates of 50.8, 26.6, 32.5, and 2.4%, respectively. Confirmed ESBL rates among *E. coli* (EC) and KSP were only 4.8 and 5.0%. Unconfirmed ESBL R was due to FOX (5) and CMY (8) in 57% of strains. The *qnr* gene was detected in only 2.5% of 283 FQR ENT strains. Among PSA, cefepime, MEM, and tobramycin had lowest R rates (5.6-7.9%). All comparator agents were >97% S against MSSA except the FQs (only 88.6-90.4%).

	Meropenem MIC (mg/L)				
Organism (no. tested)	MIC50	MIC90	Range	%S[a]	%R[a]
EC (641)	≤0.015	0.03	≤0.015-0.06	100.0	0.0
KSP (619)	0.03	0.5	≤0.015->32	91.0	8.2
PSA (606)	0.5	8	≤0.015->32	86.5	6.4
MSSA (456)	0.12	0.12	0.03-0.25	100.0	0.0
EF (149)[b]	4	8	0.5-16	-	-
SPN (138)[b]	≤0.015	1	≤0.015-1	78.3	10.1
BST (113)[b]	0.03	0.06	≤0.015-0.25	100.0	-
VGS (49)[b]	0.03	0.25	≤0.015-4	95.9	-
CSP (37)[b]	0.06	2	≤0.015-4	100.0	0.0
PEP (33)[b]	0.06	0.25	≤0.015-0.5	100.0	0.0

a. CLSI M100-S17 or M11-A6 breakpoints applied.
b. EF = *E. faecalis*, SPN = *S. pneumoniae*, BST = beta-haemolytic streptococci, VGS = viridians group streptococci, CSP = *Clostridium* spp., and PEP = *Peptostreptococcus* spp.

Conclusions: MYSTIC Program MIC results demonstrate continued CARB potency and spectrum of activity against ENT, PSA and MSSA; however, the escalating presence of serine C-ase among KSP is a serious concern. Continued surveillance in the USA MYSTIC sites appears warranted to monitor the activity of the CARBs and other broad-spectrum agents used as empiric or directed therapy against key pathogens for the treatment of serious infections.

INTRODUCTION

Antimicrobial surveillance studies can provide valuable information to clinicians about susceptibility and resistance rates of antimicrobial agents used for directed or empiric therapy of serious infections within a medical center or within a geographic region. These studies can also help monitor for changing susceptibility/resistance rates and/or dissemination of antimicrobial resistance mechanisms at the local, regional or global levels. Such studies can serve to control and minimize the spread of mobile genetic resistance markers.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program is a resistance surveillance study that monitors the in vitro activity of meropenem and comparator agents in Asia, Europe, North America and Latin America by sampling organisms from >100 participant medical centers annually. Participant sites in the United States (USA) have been monitored since 1999 using a central laboratory design (JMI Laboratories, North Liberty, Iowa, USA) to determine susceptibility and resistance rates. We report the antimicrobial susceptibility testing results from the MYSTIC Program (USA) isolates collected in 2006 when tested against meropenem and up to 10 broad-spectrum comparison agents.

MATERIALS AND METHODS

The MYSTIC Program in 2006 utilized 15 medical centers geographically dispersed across the USA. The study design defined specific quotas per medical center for *E. coli*, *Klebsiella* spp. and *P. aeruginosa* isolates among Gram-negative bacilli, and *S. aureus*, *E. faecalis*, streptococci, clostridia and peptostreptococci among Gram-positive organisms. A total of 200 bacterial isolates per study site from hospitalized patients with serious infections were collected. Methicillin-resistant *S. aureus* (MRSA) and non-faecalis enterococcal species were excluded from the study due to their intrinsic, enzyme-mediated or target site-based resistances to carbapenems and other ß-lactams. All isolates were shipped to the central reference laboratory (JMI Laboratories) for processing.

A total of 2,841 (95% compliance) isolates were processed from participating medical centers for the year. Isolate identifications were performed at each local laboratory and confirmed at the central reference laboratory using colonial morphology, biochemical tests (Remel, Lenexa, Kansas, USA) and/or the Vitek System identification cards (bioMerieux, Hazelwood, Missouri, USA), as required. All isolates were stored at -70°C in trypticase soy broth with 15% glycerol or defibrinated rabbit blood until processed further.

Susceptibility testing for the aerobic isolates was performed utilizing Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS) reference methods (M7-A7) in commercially-prepared, validated, dry-format panels (TREK Diagnostics, Ohio, USA). Breakpoint criteria from the CLSI M100-S17 document were applied for interpretation of susceptibility and resistance. Quality control (QC) was assured utilizing concurrent testing with American Type Culture Collection (ATCC) strains; all QC results within published CLSI ranges.

The anaerobic clostridial and *Peptostreptococcus* spp. isolates were tested for susceptibility utilizing CLSI agar dilution reference method to determine MICs for meropenem, imipenem, piperacillin/tazobactam and metronidazole. CLSI (M11-A7) criteria were applied for interpretation of susceptibility and resistance. All QC results for *Bacteroides fragilis* ATCC 25285 and *Eubacterium lentum* ATCC 43055 were within published CLSI ranges.

The CLSI extended-spectrum ß-lactamase (ESBL) screening criteria (MIC ≥2 mg/L for ceftazidime or ceftriaxone) were applied to *E. coli* and *Klebsiella* spp. MIC test results. Screen-positive isolates were tested by a disk approximation method and/or Etest (AB BIODISK, Solna, Sweden) ESBL strip to detect enhanced ceftazidime, cefotaxime or aztreonam activity in the presence of clavulanic acid (confirmatory tests). All *Klebsiella* spp. isolates with an elevated carbapenem MIC result (MIC, ≥2 mg/L) were screened for the presence of either a metallo-ß-lactamase or a serine carbapenemase using disk approximation methods, or the Etest metallo-ß-lactamase strip (imipenem ± EDTA), followed by PCR with sequencing. All *P. aeruginosa* isolates meeting the Senda et al. (1996) criteria of resistance to both tested carbapenems (imipenem and meropenem MIC, ≥16 mg/L) and ceftazidime (MIC, ≥32 mg/L) were further screened for the presence of a metallo-ß-lactamase (MßL) using the disk approximation method described by Arakawa et al. (2000) to demonstrate EDTA and/or 2-mercaptopropionic acid inhibition of meropenem or imipenem or ceftazidime hydrolysis.

RESULTS

- The carbapenems demonstrated the lowest resistance rates (3.3-4.0%; Table 1) against all Enterobacteriaceae isolates tested in the 2006 USA MYSTIC Program with all carbapenem resistance observed among *Klebsiella* spp., most with documented KPC-carbapenemase production.
- A total of 57 *Klebsiella* spp. isolates (9.2% overall) collected from two sites in New York City, and one site each in New Jersey and Ohio, were confirmed to possess a KPC-carbapenemase using PCR methods with medical center-specific KPC-positive rates of 50.8, 26.6, 32.5 and 2.4%, respectively (Table 2).
- Confirmed ESBL rates among *E. coli* and *Klebsiella* spp. isolates were similar to prior surveillance rates at only 4.8 and 5.0%, with the presence of FOX-5 and CMY-2 Amp-C beta-lactamases confirmed in 57% of the ESBL-screen-positive, confirmatory test negative strains. CMY-2 enzymes were identified in strains isolated from medical centers in New York (2), Utah (1), Iowa (1), Washington (1), and California (1). Fox-5 was identified in five *E. coli* strains isolated in New York (4) and Louisiana (1).
- Against all Enterobacteriaceae isolates, the fluoroquinolones had the highest resistance rates with 26.4-27.5% for *E. coli* and 16.8-17.3% for *Klebsiella* spp. (Table 1). Among the 283 fluoroquinolone-resistant Enterobacteriaceae isolates, *qnr* genes were detected in only 2.5%.

Table 1. Antimicrobial activity of meropenem and up to ten comparator agents tested against *E. coli*, *Klebsiella* species, *P. aeruginosa*, *S. aureus*, and *E. faecalis* isolates in the USA MYSTIC Program (2006).

	MIC (mg/L)			
Organism (no. tested)/ Antimicrobial agent	50%	90%	Range	% susceptible/resistant[a]
Escherichia coli (641)				
Meropenem	≤0.015	0.03	≤0.015-0.06	100.0/0.0
Imipenem	0.12	0.25	0.06-1	100.0/0.0
Ertapenem	≤0.015	≤0.015	≤0.015-1	100.0/0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	95.0/3.4 (6.9)[b]
Ceftazidime	≤0.12	0.5	≤0.12->16	95.0/3.3 (7.3)[b]
Cefepime	≤0.12	0.25	≤0.12->16	97.5/1.6
Piperacillin/Tazobactam	≤8	≤8	≤8->64	96.4/1.7
Gentamicin	≤4	>8	≤4->8	86.9/11.4
Tobramycin	≤1	8	≤1->8	86.4/9.0
Ciprofloxacin	≤0.25	>2	≤0.25->2	72.4/27.5
Levofloxacin	≤0.5	>4	≤0.5->4	72.9/26.4
Klebsiella spp.[c] (619)				
Meropenem	0.03	0.5	≤0.015->32	91.0/8.2 (8.7)[d]
Imipenem	0.25	1	0.03->32	90.6/6.8 (8.7)[d]
Ertapenem	≤0.015	2	≤0.015->32	90.1/9.5
Ceftriaxone	≤0.25	>32	≤0.25->32	85.1/10.3 (15.7)[b]
Ceftazidime	≤0.12	>16	≤0.12->16	86.4/12.9 (16.5)[b]
Cefepime	≤0.12	8	≤0.12->16	90.1/9.2
Piperacillin/Tazobactam	≤8	>64	≤8->64	84.7/14.1
Gentamicin	≤4	≤4	≤4->8	92.4/6.3
Tobramycin	≤1	>8	≤1->8	85.9/13.4
Ciprofloxacin	≤0.25	>2	≤0.25->2	81.9/17.3
Levofloxacin	≤0.5	>4	≤0.5->4	82.7/16.8
P. aeruginosa (606)				
Meropenem	0.5	8	≤0.015->32	86.5/6.4
Imipenem	1	16	0.06->32	80.2/10.7
Ceftazidime	2	>16	0.25->16	82.0/12.9
Cefepime	4	16	≤0.12->16	84.2/5.6
Piperacillin/Tazobactam	≤8	>64	≤8->64	88.6/11.4
Gentamicin	≤4	>8	≤4->8	84.2/11.7
Tobramycin	≤1	8	≤1->8	89.9/7.9
Ciprofloxacin	≤0.25	>2	≤0.25->2	73.9/20.6
Levofloxacin	≤0.5	>4	≤0.5->4	71.8/21.8
S. aureus (456)				
Meropenem	0.12	0.12	0.03-0.25	100.0/0.0
Imipenem	0.03	0.03	≤0.015-0.06	100.0/0.0
Ertapenem	0.12	0.25	0.06-1	100.0/0.0
Ceftriaxone	4	4	0.5-16	99.6/0.0
Ceftazidime	8	8	1->16	97.4/0.2
Cefepime	2	4	0.5-8	100.0/0.0
Piperacillin/Tazobactam	≤8	≤8	≤8-16	99.8/0.2
Gentamicin	≤4	≤4	≤4->8	98.7/1.1
Tobramycin	≤1	≤1	≤1->8	98.0/1.5
Ciprofloxacin	≤0.25	2	≤0.25->2	88.6/9.4
Levofloxacin	≤0.5	≤0.5	≤0.5->4	90.4/8.8
Penicillin	4	>8	≤0.06->8	21.7/78.3
E. faecalis (149)				
Meropenem	4	8	0.5-16	-/-
Imipenem	1	2	0.25-4	-/-
Piperacillin/Tazobactam	≤8	≤8	≤8-16	-/-
Gentamicin	≤500	≤500	≤500->500	76.5/23.5
Ciprofloxacin	1	>2	≤0.25->2	65.1/33.6
Levofloxacin	1	>4	≤0.5->4	66.4/33.6
Penicillin	2	4	0.5-8	100.0/0.0

a. Criteria as published by the CLSI M100-S17.
b. ESBL phenotype using CLSI screening criteria of ≥2 mg/L.
c. Includes: *Klebsiella ornithinolytica* (1 strain), *K. oxytoca* (89 strains), and *K. pneumoniae* (529 strains).
d. Bush group 2f carbapenemase screening concentration of ≥2 mg/L for meropenem or imipenem. Serine carbapenemase (KPC) production confirmed in 57 strains.

- Meropenem was eight-fold more active than imipenem against *E. coli* isolates (MIC_{90}, 0.03 vs. 0.25 mg/L), and two-fold more active against *Klebsiella* spp. (MIC_{90}, 0.5 vs. 1 mg/L) and *P. aeruginosa* (MIC_{90}, 8 vs. 16 mg/L).
- Against *P. aeruginosa* isolates, tobramycin demonstrated the highest susceptibility rate (89.9%) followed by piperacillin/tazobactam (88.6%), meropenem (86.5%) and cefepime or gentamicin (84.2%).
- All broad-spectrum antimicrobial agents demonstrated ≥97.4% susceptibility rates against oxacillin-susceptible *S. aureus* isolates, except for the fluoroquinolones with only 88.6-90.4% susceptibility.
- High-level gentamicin resistance (>500 mg/L) was observed in 23.5% of *E. faecalis* isolates and fluoroquinolone resistance was 33.6%.
- Table 3 shows that levofloxacin was the most active agent in vitro against *S. pneumoniae* isolates with a 100.0% susceptibility rate. All three carbapenems tested had nearly identical MIC_{50}, MIC_{90} and MIC result ranges, however, breakpoints used (CLSI) vary widely from those used for respiratory tract indications (>90% susceptible; cefepime, ceftriaxone, ertapenem, and levofloxacin) to very conservative lower breakpoints applied to meningitidis (78.3% for meropenem).
- All agents tested were highly active (≥97.3%) against ß-haemolytic streptococci except for three fluoroquinolone resistant strains, one each from Hawaii, Kentucky, and Washington state.
- Meropenem was highly active (MIC_{50}, 0.06 mg/L) and provided complete coverage (100.0% susceptibility) against the collection of Gram-positive anaerobic *Clostridium* and *Peptostreptococcus* species tested. In contrast, imipenem had a susceptibility rate of 86.5 against the *Clostridium* spp. isolates (Table 4).

Table 2. KPC carbapenemase-producing *Klebsiella* isolates identified within the USA MYSTIC Program (2006).

			MIC range (mg/L)	
Organism	State	# of strains/total	Meropenem	Imipenem
K. pneumoniae (56 strains)	New York	31/61	16->32	8->32
	New York	12/45	16-32	8->32
	New Jersey	13/40	4->32	8->32
K. oxytoca (1 strain)	Ohio	1/42	2	8

Table 3. Antimicrobial activity of meropenem and 11 comparison agents tested against *S. pneumoniae*, ß-haemolytic and viridans group streptococci in the USA MYSTIC Program (2006).

	MIC (mg/L)			
Organism (no. tested)/ Antimicrobial agent	50%	90%	Range	% susceptible/resistant[a]
S. pneumoniae (138)				
Meropenem	≤0.015	1	≤0.015-1	78.3/10.1
Imipenem	≤0.015	0.25	≤0.015-2	76.8/6.5
Ertapenem	≤0.015	1	≤0.015-2	98.6/0.0
Ceftriaxone	≤0.25	1	≤0.25-4	94.9/2.2
Cefepime	≤0.12	1	≤0.12-2	94.2/0.0
Levofloxacin	1	1	≤0.5-2	100.0/0.0
Penicillin	≤0.06	2	≤0.06-8	60.9/18.1
ß-haemolytic streptococci[b] (113)				
Meropenem	0.03	0.06	≤0.015-0.25	100.0/-
Imipenem	≤0.015	0.03	≤0.015-0.06	-/-
Ertapenem	0.03	0.06	≤0.015-0.5	100.0/-
Ceftriaxone	≤0.25	≤0.25	<0.25	100.0/-
Cefepime	≤0.12	≤0.12	≤0.12-0.5	100.0/-
Levofloxacin	≤0.5	1	≤0.5->4	97.3/2.7
Penicillin	≤0.06	≤0.06	≤0.06-0.12	100.0/-
Viridans group streptococci[c] (49)				
Meropenem	0.03	0.25	≤0.015-4	95.9/-
Imipenem	0.03	0.12	≤0.015-4	-/-
Ertapenem	0.06	0.5	≤0.015-8	-/-
Ceftriaxone	≤0.25	0.5	≤0.25-8	98.0/2.0
Cefepime	≤0.12	0.5	≤0.12-8	98.0/2.0
Levofloxacin	1	2	≤0.5->4	93.9/6.1
Penicillin	≤0.06	0.5	≤0.06->8	77.6/4.1

a. Criteria as published by the CLSI M100-S17.
b. Includes: Group A streptococci (39 strains), Group B streptococci (58 strains), Group C streptococci (4 strains), Group F streptococci (2 strains), and Group G streptococci (10 strains).
c. Includes: *Streptococcus anginosus* (one strain), *S. bovis* (two strains), *S. intermedius* (two strains), *S. mitis* (eight strains), *S. parasanguis* (one strain), *S. salivarius* (two strains), *S. sanguinis* (four strains), and unspecieated viridans group streptococci (29 strains).

Table 4. Antimicrobial activity of meropenem and three comparator agents tested against anaerobic Gram-positive species in the USA MYSTIC Program (2006).

	MIC (mg/L)			
Organism (no. tested)/ Antimicrobial agent	50%	90%	Range	% susceptible/resistant[a]
Clostridium spp.[b] (37)				
Meropenem	0.06	2	≤0.015-4	100.0/0.0
Imipenem	0.25	8	≤0.015-16	86.5/8.1
Metronidazole	1	2	0.12-4	100.0/0.0
Piperacillin/Tazobactam	0.5	4	≤0.12-16	100.0/0.0
Peptostreptococcus spp.[c] (33)				
Meropenem	0.06	0.25	≤0.015-0.5	100.0/0.0
Imipenem	0.12	0.25	≤0.015-1	100.0/0.0
Metronidazole	0.5	1	≤0.03->16	97.0/3.0
Piperacillin/Tazobactam	≤0.12	0.25	≤0.12-16	100.0/0.0

a. Criteria as published by the CLSI M11-A7.
b. Includes: *Clostridium bifermentans* (2 strains), *C. clostridioforme* (3 strains), *C. difficile* (8 strains), *C. innocuum* (2 strains), *C. perfringens* (14 strains), and *Clostridium* species (8 strains).
c. Includes: *Peptostreptococcus anaerobius* (1 strain), *P. asaccharolyticus* (5 strains), *P. magnus* (11 strains), *P. micros* (4 strains), *P. tetradius* (1 strain) and *Peptostreptococcus* species (11 strains).

CONCLUSIONS

- Meropenem and imipenem demonstrated a similar potency and spectrum of activity as reported earlier (1999-2005) in MYSTIC Program surveillance results against *E. coli*, *P. aeruginosa*, oxacillin-susceptible staphylococci and *E. faecalis* isolates.
- The escalating incidence and widening geographic impact of KPC carbapenemase-producing *Klebsiella* spp. isolates is a critical clinical concern and should be monitored more closely.
- Continued surveillance of Gram-negative bacilli, oxacillin-susceptible staphylococci, and Gram-positive anaerobic species appears warranted to monitor for variations being documented among the carbapenems and other broad-spectrum agents.

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