A-133

ANTIMICROBIAL POTENCY AND SPECTRUM OF MEROPENEM VERSUS ELEVEN BROAD-SPECTRUM AGENTS: REPORT FROM THE UNITED STATES (US) MYSTIC PROGRAM (2003)

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

ABSTRACT

Background: The Meropenem (MEM) Yearly Susceptibility Test Information Collection (MYSTIC) Program is a longitudinal global surveillance network of >100 sites that use carbapenems. In the US, 15 medical centers participate annually by forwarding 200 bacterial isolates to the central monitoring laboratory (JMI Laboratories, North Liberty, IA).

Methods: All bacterial strains were tested for susceptibility (S) to 12 broad-spectrum antimicrobials using National Committee for Clinical Laboratory Standards (NCCLS) reference methods and interpretive criteria. In 2003, 2,848 bacterial isolates were collected and tested for S against two carbapenems (CARB), 3 cephalosporins, aztreonam (AZT), piperacillin/tazobactam (P/T), 2 aminoglycosides, and 2 fluoroquinolones (FQ).

Results: Against 1,439 Enterobacteriaceae (ENT) strains, MEM was the most potent antimicrobial agent (MIC_{90}, 0.06 and 0.03 µg/ml, respectively). The rank order of % resistance (R) was MEM (0.0% R) < imipenem (IMP) < cefepime (CPM) < ceftriaxone < P/T < tobramycin (TOB) < AZT < ceftazidime < gentamicin < levofloxacin < ciprofloxacin (CIPRO; 8.6%). Against 621 non-fermentative Gram-negative bacilli (NFGNB; 90% *P. aeruginosa* and *Acinetobacter* spp.), MEM, IMP and TOB were the most active agents (MIC_{90}, 8 µg/ml). MEM demonstrated the highest % S rate at 87.8% followed by IMP, TOB and CPM. Against oxacillin-S staphylococci, all tested agents demonstrated >95% S rates except for FQs and AZT.

Conclusions: Year 2003 US MYSTIC Program results demonstrated the continued potent activity of the CARB class against all Gram-negative species compared to prior year results. A steady trend toward decreasing S was observed for CIPRO against ENT, NFGNB and oxacillin-S staphylococci. Continued surveillance of these antimicrobial agents appears warranted.

INTRODUCTION

In United States (US) hospital laboratories, up to 50% of all isolates recovered are Gram-negative bacilli and 80% of these belong to the Enterobacteriaceae group. Some of the resistance mechanisms in these organisms that can be monitored by antimicrobial surveillance programs include: ß-lactamases, extended-spectrum ß-lactamases (ESBLs), inhibitor-resistant ESBLs, stably derepressed AmpC cephalosporinases, K1 enzyme hyperproducers, carbapenem-hydrolyzing ß-lactamases, DNA gyrase mutants, and topoisomerase alterations. The carbapenems have demonstrated the broadest antibacterial spectrum of the ß-lactam agents available for therapy and retain activity against isolates producing ESBL, AmpC, K1, PER and other enzymes.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program is a global, longitudinal antimicrobial resistance surveillance program initiated in 1997 (1999 in the US) to perform post-market surveillance and monitor the continued potency and spectrum of meropenem. Regional monitoring is performed in Europe, North America, Latin America, and the Asia-Pacific with greater than 125 participating medical centers, representing more than 30 countries. The MYSTIC Program participant sites are medical centers actively utilizing meropenem for the treatment of serious infections.

In this study, we report on the antimicrobial activity of meropenem and 11 comparator broad-spectrum antimicrobial agents tested against groups of bacterial pathogens collected in 2003 within the MYSTIC Program. Included in this monitored year was the market leading fluoroquinolone, levofloxacin. These susceptibility results can be used to assist participant institutions with empiric treatment choices and to compare local resistance rates to national and international resistance frequencies.

MATERIALS AND METHODS

Participant Centers: Fifteen medical centers geographically distributed across the United States participated in the MYSTIC Program in 2003. All medical centers continued participation from the previous year and included six of the original 10 centers recruited in 1999.

Bacterial Isolates: Each center was requested to submit 140 Gram-negative and 60 Gram-positive aerobic strains isolated from serious infections to the central monitoring laboratory (JMI Laboratories, North Liberty, IA). Organism identifications were confirmed by colony morphology, biochemical tests and/or the Vitek System (bioMerieux, Hazelwood, MO). Only those isolates from species with known intrinsic mechanisms of resistance to carbapenems were excluded (*Enterococcus* species, oxacillin-resistant staphylococci, and *Stenotrophomonas maltophilia*). A total of 2,060 Gram-negative bacilli and 788 Gram-positive isolates were processed.

MATERIALS AND METHODS CONTINUED

Susceptibility Testing: Isolates were tested using National Committee for Clinical Laboratory Standards (NCCLS) reference methods with minimum inhibitory concentrations (MICs) being determined by procedures in M7-A6. MIC results were determined for meropenem, imipenem, ceftriaxone, ceftazidime, cefepime, aztreonam, ciprofloxacin, levofloxacin, piperacillin/tazobactam, gentamicin, tobramycin and oxacillin (*Staphylococcus* only). Susceptibility and resistance was determined by NCCLS interpretive criteria published in M100-S14. NCCLS screening criteria (MIC, ≥ 2 µg/ml against ceftazidime or ceftriaxone or aztreonam) for the presence of ESBL enzymes were applied to *Escherichia coli* and *Klebsiella* spp. Each screen-positive isolate was tested with a disk approximation method to show a synergistic clavulanic acid effect with either ceftazidime or cefotaxime. The Senda et al. [1996] criteria for resistance to carbapenems (MIC, > 8 µg/ml) and ceftazidime (MIC, > 16 µg/ml) were applied to *Pseudomonas aeruginosa* and *Acinetobacter* spp. to screen for the presence of metallo-ß-lactamase (MßL) enzymes. Confirmation of a MßL was performed with a disk approximation method using imipenem and meropenem demonstrating a synergistic effect with EDTA or 2-mercaptopropionic acid. Quality control was assured by concurrent testing with American Type Culture Collection (ATCC) strains including *Enterococcus faecalis* ATCC 29212, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619.

RESULTS

- The two carbapenems demonstrated an excellent spectrum of activity for all Enterobacteriaceae species and groups, with only one strain (*Klebsiella oxytoca*) showing resistance to imipenem. Imipenem was routinely the least active carbapenem with meropenem four- to 32-fold more active by weight (Table 1).
- The rank order of susceptibility against all Enterobacteriaceae isolates tested was: meropenem = imipenem (100.0% susceptible) > cefepime (99.6%) > piperacillin/tazobactam (95.5%) > ceftriaxone (95.4%) > aztreonam (94.8%) > ceftazidime = tobramycin (94.7%) > gentamicin (94.3%) > levofloxacin (91.0%) > ciprofloxacin (89.9%; Table 1).
- The fluoroquinolones consistently demonstrated the lowest percent susceptibility rates of all the agents tested (3.0 - 10.9% resistance), with *P. mirabilis*, *E. coli* and *Enterobacter* spp. isolates falling below 90.0% (Table 1).
- Both ceftazidime and aztreonam demonstrated reduced activity against *Enterobacter* isolates (15.2% resistance) secondary to the hyper-expression of AmpC enzymes (Table 1).
- A total of 2.1% of *E. coli* and 8.6% of *Klebsiella* species met NCCLS screening criteria for the presence of an ESBL. Sixteen of the 40 (40%) ESBL-screen-positive isolates demonstrated an inhibition by clavulanate and were confirmed as ESBL-producers. All ESBL-containing isolates were susceptible to the carbapenems.
- Against non-fermentative Gram-negative bacilli, only piperacillin/tazobactam against *P. aeruginosa* and imipenem against *Acinetobacter* species demonstrated greater than 90.0% susceptibility rates (Table 2). Meropenem was more potent than imipenem against *P. aeruginosa* isolates with a two- to eight-fold lower MIC50 and MIC90, and 3.7 - 59.0% greater susceptibility rate. Against the *Acinetobacter* species, imipenem was two-fold more potent than meropenem.
- The combined rank order of susceptibility results for antimicrobial agents tested against the non-fermentative Gram-negative bacilli was: meropenem (87.8%) > imipenem (85.5%) > tobramycin (85.3%) > cefepime (80.2%) > ceftazidime (79.4%) > gentamicin (78.7%) > piperacillin/tazobactam (78.1%) > ciprofloxacin (65.2%) > levofloxacin (63.8%) > aztreonam (51.7%) > ceftriaxone (18.8%; Table 2).
- All carbapenems and piperacillin/tazobactam were uniformly active against oxacillin-susceptible *S. aureus* and coagulase-negative staphylococci (Table 3).
- Ceftriaxone and cefepime showed comparable susceptibility rates (> 99.0% susceptibility). Significantly lower susceptibility rates were observed for ceftazidime (95.4 - 97.2%) and the aminoglycosides (94.7 - 98.2%) against all staphylococci isolates tested.
- Against *S. pneumoniae*, only one strain (0.6%) was fluoroquinolone-resistant and none of the isolates were cephalosporin-resistant (Table 3). Imipenem was two-fold more potent than meropenem against the pneumococci.

Table 1. Antimicrobial activity of meropenem compared to 10 broad-spectrum antimicrobial agents tested against 1,358 Enterobacteriaceae (MYSTIC Program, 2003).

Organism/Antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% susceptible/resistant[a]
Citrobacter spp. (141)[b]				
Meropenem	0.03	0.03	≤0.016-4	100.0/0.0
Imipenem	0.25	0.5	0.03-4	100.0/0.0
Ceftriaxone	≤0.25	32	≤0.25->32	83.7/6.4
Ceftazidime	0.25	>16	≤0.12->16	84.4/14.2
Cefepime	≤0.12	1	≤0.12->16	99.3/0.7
Aztreonam	≤1	>16	≤1->16	83.7/12.8
Piperacillin/Tazobactam	2	16	≤1->128	90.8/5.0
Gentamicin	≤1	1	≤1->8	90.8/8.5
Tobramycin	≤1	2	≤1->8	93.6/5.7
Ciprofloxacin	≤0.25	1	≤0.25->2	91.5/7.1
Levofloxacin	≤0.06	2	≤0.06->8	92.2/4.3
Enterobacter spp. (158)[c]				
Meropenem	0.03	0.12	≤0.016-2	100.0/0.0
Imipenem	0.25	1	0.12-2	100.0/0.0
Ceftriaxone	≤0.25	32	≤0.25->32	81.6/8.9
Ceftazidime	0.25	>16	≤0.12->16	77.2/15.2
Cefepime	≤0.12	2	≤0.12->16	97.5/1.3
Aztreonam	≤1	>16	≤1->16	76.6/15.2
Piperacillin/Tazobactam	2	32	≤1->128	84.8/6.3
Gentamicin	≤1	2	≤1->8	90.5/7.6
Tobramycin	≤1	2	≤1->8	91.8/5.1
Ciprofloxacin	≤0.25	2	≤0.25->2	88.0/9.5
Levofloxacin	≤0.06	4	≤0.06->8	89.2/5.7
E. coli (469)				
Meropenem	≤0.016	0.03	≤0.016-0.12	100.0/0.0
Imipenem	0.12	0.12	0.03-1	100.0/0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	99.6/0.2(1.1)[d]
Ceftazidime	≤0.12	0.25	≤0.12->16	99.6/0.4(1.1)[d]
Cefepime	≤0.12	≤0.12	≤0.12-4	100.0/0.0
Aztreonam	≤1	≤1	≤1-8	100.0/0.0(2.1)[d]
Piperacillin/Tazobactam	≤1	2	≤1->128	98.3/1.3
Gentamicin	≤1	2	≤1->8	96.6/2.8
Tobramycin	≤1	2	≤1->8	97.0/1.3
Ciprofloxacin	≤0.25	>2	≤0.25->2	89.1/10.9
Levofloxacin	≤0.06	8	≤0.06->8	89.1/10.2
Klebsiella spp. (303)[e]				
Meropenem	0.03	0.03	≤0.016-8	99.7/0.0
Imipenem	0.12	0.25	0.06-16	99.7/0.3
Ceftriaxone	≤0.25	0.5	≤0.25->32	96.7/0.7(7.6)[d]
Ceftazidime	≤0.12	0.5	≤0.12->16	95.4/4.0(6.9)[d]
Cefepime	≤0.12	0.25	≤0.12->16	99.7/0.3
Aztreonam	≤1	≤1	≤1->16	95.4/4.3(8.6)[d]
Piperacillin/Tazobactam	2	8	≤1->128	94.4/3.0
Gentamicin	≤1	≤1	≤1->8	93.7/4.3
Tobramycin	≤1	≤1	≤1->8	93.1/4.6
Ciprofloxacin	≤0.25	0.5	≤0.25->2	95.0/4.6
Levofloxacin	≤0.06	0.5	≤0.06->8	95.4/3.6
P. mirabilis (154)				
Meropenem	0.06	0.06	≤0.016-0.12	100.0/0.0
Imipenem	0.5	2	0.12-4	100.0/0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0/0.0
Ceftazidime	≤0.12	≤0.12	≤0.12-0.5	100.0/0.0
Cefepime	≤0.12	≤0.12	≤0.12-1	100.0/0.0
Aztreonam	≤1	≤1	≤1	100.0/0.0
Piperacillin/Tazobactam	≤1	≤1	≤1-2	100.0/0.0
Gentamicin	≤1	2	≤1->8	93.5/5.8
Tobramycin	≤1	2	≤1->8	94.2/1.3
Ciprofloxacin	≤0.25	>2	≤0.25->2	85.1/10.4
Levofloxacin	≤0.06	4	≤0.06->8	89.6/7.8
Serratia spp. (133)[f]				
Meropenem	0.03	0.06	0.03-0.12	100.0/0.0
Imipenem	0.5	1	0.25-2	100.0/0.0
Ceftriaxone	≤0.25	0.5	≤0.25->32	98.5/0.8
Ceftazidime	≤0.12	0.25	≤0.12->16	99.2/0.8
Cefepime	≤0.12	0.25	≤0.12-2	100.0/0.0
Aztreonam	≤1	≤1	≤1->16	99.2/0.8
Piperacillin/Tazobactam	≤1	4	≤1-32	97.7/0.0
Gentamicin	≤1	≤1	≤1->8	99.2/0.8
Tobramycin	2	4	≤1->8	97.0/2.3
Ciprofloxacin	≤0.25	0.5	≤0.25->2	93.2/3.8
Levofloxacin	0.12	1	≤0.06-8	95.5/3.0

a. Criteria as published by the NCCLS [2004].
b. Includes *C. amalonaticus* (six strains), *C. braakii* (one strain), *C. freundi* (86 strains), *C. koseri* (33 strains), *C. youngae* (one strain), and *Citrobacter* spp. (14 strains).
c. Includes *E. aerogenes* (46 strains), *E. cloacae* (94 strains), *E. taylorae* (one strain), and *Enterobacter* spp. (17 strains).
d. Percentage of ESBL phenotypes using the NCCLS screening concentration of ≥ 2 µg/ml for ceftriaxone or ceftazidime or aztreonam.
e. Includes *K. oxytoca* (46 strains), *K. ozaenae* (one strain), *K. pneumoniae* (235 strains) and *Klebsiella* spp. (21 strains).
f. Includes *S. liquifaciens* (three strains), *S. marcescens* (112 strains), *S. odorifera* (one strain), *S. rubidaea* (one strain) and *Serratia* spp. (16 strains).

Table 2. Antimicrobial activity of meropenem compared to 10 broad spectrum antimicrobial agents tested against 565 non-fermentative Gram-negative bacilli (MYSTIC Program, 2003).

Organism/Antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% susceptible/resistant[a]
P. aeruginosa (454)				
Meropenem	0.5	8	≤0.016->32	88.3/7.3
Imipenem	1	8	0.03-32	84.6/9.5
Ceftriaxone	>32	>32	0.5->32	11.9/63.0
Ceftazidime	2	>16	0.25->16	83.7/10.8
Cefepime	4	16	0.25>16	85.7/6.2
Aztreonam	8	>16	≤1->16	65.4/16.5
Piperacillin/Tazobactam	4	64	≤1->128	90.3/9.7
Gentamicin	2	>8	≤1->8	84.6/11.0
Tobramycin	≤1	8	≤1->8	89.4/9.5
Ciprofloxacin	≤0.25	>2	≤0.25->2	68.7/25.3
Levofloxacin	0.5	>8	≤0.06->8	65.6/26.0
Acinetobacter spp. (111)[b]				
Meropenem	0.5	8	0.03-32	87.4/7.2
Imipenem	0.25	4	0.03-16	91.9/1.8
Ceftriaxone	16	>32	≤0.25->32	36.0/35.1
Ceftazidime	8	>16	0.25->16	64.0/32.4
Cefepime	8	>16	≤0.12->16	63.1/18.0
Aztreonam	>16	>16	≤1->16	8.1/67.6
Piperacillin/Tazobactam	8	128	≤1->128	61.3/16.2
Gentamicin	≤1	>8	≤1->8	63.1/32.4
Tobramycin	≤1	>8	≤1->8	82.0/11.7
Ciprofloxacin	0.5	>2	≤0.25->2	58.6/40.5
Levofloxacin	0.25	>8	≤0.06->8	60.4/36.0

a. Criteria as published by the NCCLS [2004].
b. Includes *A. baumannii* (73 strains), *A. junii* (one strain), *A. lwoffii* (nine strains), and *Acinetobacter* spp. (28 strains).

Table 3. Activity of 10 antimicrobial agents tested against 778 Gram-positive cocci in the MYSTIC Program (2003).

Organism/Antimicrobial agent (no. tested)	MIC (µg/ml) 50%	90%	Range	% susceptible/resistant[a]
Oxacillin-susceptible *S. aureus* (284)				
Meropenem	0.12	0.12	0.06-0.5	100.0/0.0
Imipenem	0.03	0.03	≤0.016-0.12	100.0/0.0
Ceftriaxone	4	4	0.5-8	100.0/0.0
Ceftazidime	8	8	2-16	97.2/0.0
Cefepime	2	4	0.5-4	100.0/0.0
Piperacillin/Tazobactam	≤1	2	≤1-2	100.0/0.0
Gentamicin	≤1	≤1	≤1->8	98.2/1.4
Tobramycin	≤1	≤1	≤1->8	94.7/4.2
Ciprofloxacin	≤0.25	1	≤0.25->2	91.5/6.7
Levofloxacin	0.12	0.5	≤0.06->8	94.0/3.9
Oxacillin-susceptible CoNS (173)[b]				
Meropenem	0.06	0.12	0.03-0.5	100.0/0.0
Imipenem	≤0.016	≤0.016	≤0.016-0.06	100.0/0.0
Ceftriaxone	1	4	0.5-16	99.4/0.0
Ceftazidime	4	8	2->16	95.4/0.6
Cefepime	0.5	2	≤0.12-16	99.4/0.0
Piperacillin/Tazobactam	≤1	≤1	≤1-2	100.0/0.0
Gentamicin	≤1	≤1	≤1->8	96.0/1.2
Tobramycin	≤1	2	≤1->8	97.1/1.7
Ciprofloxacin	≤0.25	>2	≤0.25->2	82.1/17.9
Levofloxacin	0.25	8	≤0.06->8	83.8/13.3
S. pneumoniae (157)				
Meropenem	≤0.016	0.5	≤0.016-1	83.4/6.4
Imipenem	≤0.016	0.25	≤0.016-1	85.4/1.3
Ceftriaxone	≤0.25	1	≤0.25-2	94.9/0.0
Cefepime	≤0.12	1	≤0.12-2	96.2/0.0
Levofloxacin	1	1	0.5->8	99.4/0.6
Other *Streptococcus* spp. (164)[c]				
Meropenem	0.03	0.06	≤0.016-4	98.8/-[d]
Imipenem	≤0.016	0.03	≤0.016-1	-/-
Ceftriaxone	≤0.25	≤0.25	≤0.25-16	98.2/0.6
Cefepime	≤0.12	≤0.12	≤0.12-8	98.2/1.8
Levofloxacin	0.5	1	≤0.06-2	100.0/0.0

a. Criteria as published by the NCCLS [2004].
b. Includes *S. capitis* (five strains), *S. epidermidis* (29 strains), *S. haemolyticus* (five strains), *S. hominis* (four strains), *S. schleiferi* (one strain), *S. warneri* (one strain), and CoNS (128 strains).
c. Includes ß-haemolytic Streptococcus spp. (135 strains), viridans group streptococci (28 strains) and *S. bovis* (one strain).
d. - = no interpretive criteria for this category.

CONCLUSIONS

- The MYSTIC Program (US) 2003 surveillance sample from 15 participant sites demonstrated the continued, wide spectrum and high potency of meropenem, especially against Enterobacteriaceae and non-fermentative Gram-negative bacilli.
- There has been no significant increase in carbapenem resistance among Gram-negative bacilli or Gram-positive isolates over the five-year monitored period (1999-2003).
- The carbapenems (meropenem > imipenem) were fully active against ESBL- and AmpC-producing enteric bacilli, and monitoring for the possible emergence of MßLs should continue within medical centers actively utilizing carbapenems for the treatment of serious infections.

MYSTIC PROGRAM SITES

Arkansas Children's Hospital (R Jacobs/T Beavers-May); Christiana Care (L Steele-Moore); Columbia Presbyterian Medical Center (P Della-Latta); Creighton University, St. Joseph Hospital (S Cavalieri/M Hostetter); Denver Health Medical Center (M Wilson/A Graepler); Iowa Methodist Medical Center (A Herring/L Roller); Kaiser Permanente Medical Group (J Fusco); Ochsner Clinic Foundation (G Pankey/D Ashcraft); University Hospitals of Cleveland (M Jacobs/S Bajaksouzian); University of Kentucky Hospital (J Ribes/S Overman); University of Texas, MD Anderson Cancer Center (K Rolston/R Prince); University of Utah, ARUP Laboratories, Inc. (A Croft); Veterans' Affairs Medical Center, Portland (D Sewell); Vanderbilt Medical Center (C Stratton/R Verrall); and Winthrop University Hospital (P Schoch).

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