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Antimicrobial Potency and Spectrum of Activity for Meropenem: Report from the USA MYSTIC Surveillance Programme (2005)

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

AMENDED ABSTRACT

Objective
To monitor the activity of meropenem (MEM) and 10 broad-spectrum comparison agents against pathogens collected from hospitalized patients within United States (USA) medical centers participating in the Meropenem Yearly Test Information Collection (MYSTIC) Programme, a global longitudinal surveillance network of >100 medical centers actively using carbapenems worldwide. In the USA, 15 sites participated by submitting up to 200 consecutive, non-duplicate clinical isolates from serious infections.
Methods
A total of 2,910 isolates (97% compliance) including 1,657 Enterobacteriaceae (ENT), 836 non-fermentative Gram-negative bacilli (NFGB), and 417 oxacillin-susceptible staphylococci were tested at a central monitoring laboratory using CLSI reference broth microdilution susceptibility (S) methods with interpretative criteria. Ribotyping (RT) and pulsed-field gel electrophoresis (PFGE) were performed on multi-drug resistant (R) strains to determine possible clonal dissemination contribution to R patterns.
Results
Against the ENT isolates, the carbapenems demonstrated the greatest susceptibility (S; >98.7%) and all other agents, except the fluoroquinolones (FQ; 83.9-84.9% S) showed >90% S. Sixty-six *E. coli* (EC) and *Klebsiella* spp. isolates producing ESBLs (7.0%) were submitted from 12 sites, and 24 clonally related (RT 105.497.1) *K. pneumoniae* strains were identified that produced a KPC carbapenemase, and an additional strain with a SME type carbapenemase was detected from one site. FQ-R was most prevalent in indole-positive *Proteae* and EC strains with six epidemic/endemic clusters identified. Piperacillin/tazobactam, tobramycin and MEM were the most active agents (>87.6% S) against the 589 *P. aeruginosa* (PSA) isolates. Against the 125 *Acinetobacter* spp. isolates only tobramycin, imipenem and MEM demonstrated >85.6% S, all other agents were less than 72.0% S.
Conclusions
These 2005 MYSTIC Program results demonstrate the continued high activity of MEM against ENT, PSA, and oxacillin-susceptible staphylococci (MIC_{90}, 0.12 mg/L), but the rising incidence of clonally-related carbapenemases (KPC-2 and -3) among ENT is a concern. Continued surveillance within these USA participant sites appears warranted to monitor the residual activity of the important carbapenem class as well as other broad-spectrum agents against key nosocomial pathogens compared to the 6 prior years; only FQ-R rates continued to significantly progress.

INTRODUCTION

Surveillance studies are necessary to help monitor for emerging resistance occurrence rates or dissemination of an antimicrobial resistance mechanism within a local region or on a global scale. Such studies can aid in the control and minimize the spread of resistance mechanisms, and thus provide valuable information to clinicians when selecting empiric therapy for the treatment of serious infections at their medical center.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Programme is an international resistance surveillance study with greater than 100 participant sites worldwide located in Europe, North America, Latin America and Asia that was designed to monitor the in vitro activity of meropenem and other broad-spectrum antimicrobial agents in hospitals utilizing carbapenems. Participant sites have been monitored in the United States (USA) by a central laboratory design (JMI Laboratories, North Liberty, Iowa, USA) since 1999 using reference broth microdilution susceptibility testing methods to determine susceptibility and resistance rates. We report the antimicrobial susceptibility testing results from the MYSTIC Programme (USA) isolates collected in 2005, tested against meropenem and 10 other broad-spectrum agents.

MATERIALS AND METHODS

Specimen collection:
The MYSTIC Programme utilized 15 medical centers geographically dispersed across the USA with a high priority for continued longitudinal participation. The study protocol outlined specific quotas per medical center among Enterobacteriaceae and non-fermentative Gram-negative species, as well as staphylococci, for a total of 200 bacterial isolates per site from serious infections in hospitalized patients. *Stenotrophomonas maltophilia* and methicillin-resistant staphylococci were excluded from the collection due to the intrinsic resistances to carbapenems present in these species. All isolates were shipped to the central processing laboratory (JMI Laboratories) on provided transport swabs.

A total of 2,910 isolates (97.0% compliance) were submitted from the participant sites in 2005 (range 115 to 230 isolates/site). Identification of the strains were performed locally and confirmation at the central monitoring laboratory was achieved using colonial morphology, biochemical tests (Remel, Lenexa, Kansas, USA) and/or the Vitek System identification cards (bioMerieux, Hazelwood, Missouri, USA), as required.

Susceptibility testing:
Testing was performed using commercially prepared, validated dry-form panels (TREK Diagnostics, Cleveland, Ohio, USA) for all strains using Clinical and Laboratory Standards Institute (CLSI) reference methods to determine MIC values for the tested antimicrobial agents (meropenem, imipenem, aztreonam, cefepime, ceftazidime, ceftriaxone, piperacillin/tazobactam, gentamicin, tobramycin, ciprofloxacin and levofloxacin). Interpretation of susceptibility was based on published CLSI criteria (M100-S16). Quality control was assured utilizing appropriate American Type Culture Collection (ATCC) strains.

The CLSI ESBL screening criteria (MIC, ≥ 2 mg/L for ceftazidime or ceftriaxone or aztreonam) were applied to *E. coli, Klebsiella* spp. and *Proteus mirabilis* to determine phenotypic ESBL rates. All screen-positive isolates were confirmed using the disk approximation or Etest ESBL strip (AB BIODISK, Solna, Sweden) methods.

Evidence for clonality was assessed by using an automated ribotyping system (Riboprinter™ Microbial Characterization System, Qualicon, DE, USA) followed by CHEF-DRII pulsed-field gel electrophoresis (PFGE; BioRad Laboratories, CA, USA) for further epidemiologic discrimination, when necessary.

RESULTS

- Among Enterobacteriaceae, the carbapenems had the highest overall susceptibility rate (≥ 98.7%) followed by cefepime (97.6%) and piperacillin/tazobactam (92.0%; Table 1). Meropenem was four- to 16-fold more potent than imipenem for the Enterobacteriaceae species groups when comparing MIC_{90} results.
- Lowest susceptibility rates were observed for the fluoroquinolones (83.9 – 84.9%) against the Enterobacteriaceae isolates with the indole-positive Proteae and *E. coli* having the greatest resistance rates (20.4 – 36.5%).
- Extended-spectrum ß-lactamase production was confirmed in *Klebsiella* spp. (48; 10.7%), *E. coli* (18; 3.7%), *Enterobacter* spp. (6; 3.8%), *Citrobacter* spp. (3; 2.1%) and *Serratia* spp. (3; 2.2%), data not shown.
- Eighteen *Klebsiella pneumoniae* isolates from two medical centers in the same geographic region (New York) were identified with KPC-2 carbapenemases; these isolates were clonally related sharing a common ribogroup pattern (105.491.1).
- The presence of KPC carbapenemases were also identified in four *Citrobacter* spp. and two *E. coli* isolates from the same medical centers. One additional isolate of *Serratia marcescens* from a Washington state medical center was identified with a SME-1 carbapenemase (Bush group 2f).
- Among *P. aeruginosa* isolates (589 strains), piperacillin/tazobactam demonstrated the highest susceptibility rate (91.0%) followed by gentamicin (88.6%) and meropenem (86.6%). Lowest percent susceptibility was observed for ceftriaxone (17.7%) and the fluoroquinolones (69.4 - 72.5%; Table 1).
- Only tobramycin (92.0%), imipenem (92.0%) and meropenem (85.6%) demonstrated acceptable susceptibility rates for the *Acinetobacter* spp. isolates tested (Table 1).
- No metallo-ß-lactamase-producing strains were detected in the 2005 USA MYSTIC Programme.
- Among the oxacillin-susceptible staphylococci, the carbapenems, cefepime and piperacillin/tazobactam provided 100% coverage at CLSI breakpoints, while ciprofloxacin (91.4 - 87.9%) and levofloxacin (92.6 - 87.9%) had the lowest susceptibility rates against *S. aureus* and coagulase-negative staphylococci, respectively (Table 2).

Table 1. Antimicrobial activity of meropenem and 10 broad-spectrum comparator agents tested against Gram-negative bacilli studied as part of the USA MYSTIC Programme (2005).

Organism (no. tested)/ Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% susceptible/resistant[a]
Enterobacteriaceae (1,657)				
Meropenem	0.03	0.06	≤0.016->32	98.7/1.1
Imipenem	0.12	1	0.03->32	98.9/0.5
Aztreonam	≤1	8	≤1->16	90.6/7.2
Ceftriaxone	≤0.25	8	≤0.25->32	91.2/5.2
Ceftazidime	≤0.12	8	≤0.12->16	90.4/8.4
Cefepime	≤0.12	0.5	≤0.12->16	97.6/1.4
Piperacillin/Tazobactam	2	16	≤1->128	92.0/5.0
Gentamicin	≤1	4	≤1->8	90.5/7.4
Tobramycin	≤1	4	≤1->8	90.5/6.9
Ciprofloxacin	≤0.25	>2	≤0.25->2	83.9/14.8
Levofloxacin	≤0.06	8	≤0.06->8	84.9/13.2
Citrobacter spp. (146)				
Meropenem	0.03	0.06	≤0.016-2	100.0/0.0
Imipenem	0.25	1	0.06-4	100.0/0.0
Aztreonam	≤1	>16	≤1->16	80.8/10.3
Ceftriaxone	≤0.25	32	≤0.25->32	81.5/6.8
Ceftazidime	0.25	>16	≤0.12->16	80.1/19.2
Cefepime	≤0.12	1	≤0.12-16	98.6/0.0
Piperacillin/Tazobactam	2	32	≤1->128	85.6/6.8
Gentamicin	≤1	4	≤1->8	91.8/6.2
Tobramycin	≤1	4	≤1->8	91.1/6.2
Ciprofloxacin	≤0.25	1	≤0.25->2	90.4/6.2
Levofloxacin	≤0.06	2	≤0.06->8	90.4/4.8
Enterobacter spp. (160)				
Meropenem	0.03	0.06	≤0.016-16	99.4/0.6
Imipenem	0.25	1	0.06-8	99.4/0.0
Aztreonam	≤1	>16	≤1->16	76.3/16.3
Ceftriaxone	≤0.25	>32	≤0.25->32	78.8/14.4
Ceftazidime	0.25	>16	≤0.12->16	76.3/21.9
Cefepime	≤0.12	2	≤0.12-16	96.9/0.0
Piperacillin/Tazobactam	2	64	≤1->128	83.1/7.5
Gentamicin	≤1	≤1	≤1->8	92.5/6.9
Tobramycin	≤1	2	≤1->8	91.9/8.1
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	94.4/4.4
Levofloxacin	≤0.06	0.5	≤0.06->8	96.3/3.8
Escherichia coli (491)				
Meropenem	≤0.016	0.03	≤0.016-2	100.0/0.0
Imipenem	0.12	0.12	0.03-2	100.0/0.0
Aztreonam	≤1	≤1	≤1->16	95.5/3.1 (8.4)[b]
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	94.7/2.6 (6.3)[b]
Ceftazidime	≤0.12	0.5	≤0.12->16	95.1/3.1 (7.3)[b]
Cefepime	≤0.12	0.25	≤0.12->16	98.4/1.4
Piperacillin/Tazobactam	≤1	4	≤1->128	95.3/2.4
Gentamicin	≤1	>8	≤1->8	88.8/10.2
Tobramycin	≤1	4	≤1->8	91.0/5.9
Ciprofloxacin	≤0.25	>2	≤0.25->2	78.2/21.6
Levofloxacin	≤0.06	>8	≤0.06->8	78.8/20.4
Klebsiella spp. (450)				
Meropenem	0.03	0.03	≤0.016->32	96.0/3.6
Imipenem	0.12	0.25	0.03->32	96.2/1.6
Aztreonam	≤1	>16	≤1->16	85.8/13.1 (15.8)[b]
Ceftriaxone	≤0.25	16	≤0.25->32	88.7/8.2 (14.4)[b]
Ceftazidime	≤0.12	>16	≤0.12->16	87.1/12.4 (15.8)[b]
Cefepime	≤0.12	2	≤0.12->16	94.7/3.6
Piperacillin/Tazobactam	2	128	≤1->128	87.6/10.9
Gentamicin	≤1	2	≤1->8	91.3/5.8
Tobramycin	≤1	>8	≤1->8	86.9/10.7
Ciprofloxacin	≤0.25	>2	≤0.25->2	85.1/14.0
Levofloxacin	≤0.06	>8	≤0.06->8	86.2/12.4
Proteus mirabilis (147)				
Meropenem	0.06	0.06	≤0.016-0.12	100.0/0.0
Imipenem	0.5	1	0.06-2	100.0/0.0
Aztreonam	≤1	≤1	≤1	100.0/0.0 (0.0)[b]
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/0.0 (0.0)[b]
Ceftazidime	≤0.12	≤0.12	≤0.12-0.25	100.0/0.0 (0.0)[b]
Cefepime	≤0.12	≤0.12	≤0.12-0.5	100.0/0.0
Piperacillin/Tazobactam	≤1	≤1	≤1	100.0/0.0
Gentamicin	≤1	4	≤1->8	92.5/3.4
Tobramycin	≤1	2	≤1->8	96.6/0.7
Ciprofloxacin	≤0.25	2	≤0.25->2	83.0/15.6
Levofloxacin	≤0.06	2	≤0.06->8	84.4/11.6
Indole-Positive Proteae (96)				
Meropenem	0.06	0.12	≤0.016-0.12	100.0/0.0
Imipenem	1	2	0.06-2	100.0/0.0
Aztreonam	≤1	≤1	≤1-8	100.0/0.0
Ceftriaxone	≤0.25	1	≤0.25-8	100.0/0.0
Ceftazidime	≤0.12	8	≤0.12->16	95.8/2.1
Cefepime	≤0.12	≤0.12	≤0.12-8	100.0/0.0
Piperacillin/Tazobactam	≤1	2	≤1-16	100.0/0.0
Gentamicin	≤1	>8	≤1->8	80.2/14.6
Tobramycin	≤1	8	≤1->8	87.5/6.3
Ciprofloxacin	≤0.25	>2	≤0.25->2	59.4/36.5
Levofloxacin	0.5	>8	≤0.06->8	60.4/33.3
Serratia spp. (134)				
Meropenem	0.03	0.06	≤0.016-32	99.3/0.7
Imipenem	0.5	1	0.12->32	99.3/0.7
Aztreonam	≤1	≤1	≤1->16	97.8/2.2
Ceftriaxone	≤0.25	0.5	≤0.25->32	95.5/1.5
Ceftazidime	≤0.12	0.25	≤0.12->16	97.8/2.2
Cefepime	≤0.12	0.25	≤0.12->16	99.3/0.7
Piperacillin/Tazobactam	≤1	4	≤1-64	97.8/0.0
Gentamicin	≤1	2	≤1->8	94.8/3.7
Tobramycin	≤1	4	≤1->8	92.5/6.0
Ciprofloxacin	≤0.25	1	≤0.25->2	96.3/1.5
Levofloxacin	0.12	1	≤0.06-8	98.5/0.7
P. aeruginosa (589)				
Meropenem	0.5	8	≤0.016->32	87.6/6.8
Imipenem	1	8	0.03->32	84.4/7.3
Aztreonam	8	>16	≤1->16	74.2/12.2
Ceftriaxone	>32	>32	≤0.25->32	17.7/53.5
Ceftazidime	2	16	0.25->16	86.9/9.8
Cefepime	4	16	0.5->16	86.9/4.8
Piperacillin/Tazobactam	4	64	≤1->128	91.0/9.0
Gentamicin	≤1	>8	≤1->8	83.9/12.1
Tobramycin	≤1	>8	≤1->8	88.6/10.4
Ciprofloxacin	≤0.25	>2	≤0.25->2	72.5/22.4
Levofloxacin	0.5	>8	≤0.06->8	69.4/22.4
Acinetobacter spp. (125)				
Meropenem	0.5	8	≤0.016->32	85.6/8.0
Imipenem	0.25	4	≤0.016-16	92.0/3.2
Aztreonam	>16	>16	8->16	12.0/59.2
Ceftriaxone	16	>32	1->32	31.2/35.2
Ceftazidime	4	>16	0.5->16	60.8/33.6
Cefepime	4	>16	≤0.12->16	64.0/22.4
Piperacillin/Tazobactam	16	>128	≤1->128	59.2/28.8
Gentamicin	≤1	>8	≤1->8	72.0/26.4
Tobramycin	≤1	4	≤1->8	92.0/5.6
Ciprofloxacin	≤0.25	>2	≤0.25->2	60.0/40.0
Levofloxacin	0.25	>8	≤0.06->8	62.4/29.6

a. Criteria as published by the CLSI M100-S16 (2006).
b. ESBL phenotype using CLSI screening criteria of ≥ 2 mg/L for ceftriaxone or ceftazidime or aztreonam.

Table 2. Antimicrobial activity of meropenem tested against oxacillin-susceptible staphylococci (2005).

Organism (no. tested)/ Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% susceptible/resistant[a]
S. aureus (326)				
Meropenem	0.12	0.12	0.06-0.25	100.0/0.0
Imipenem	≤0.016	0.03	≤0.016-06	100.0/0.0
Aztreonam	>16	>16	≤1->16	-/-
Ceftriaxone	4	4	1-8	100.0/0.0
Ceftazidime	8	8	4-16	97.9/0.0
Cefepime	2	4	0.5-4	100.0/0.0
Pip/Tazo	≤1	2	≤1-2	100.0/0.0
Gentamicin	≤1	≤1	≤1->8	98.5/0.9
Tobramycin	≤1	≤1	≤1->8	96.3/1.5
Ciprofloxacin	≤0.25	1	≤0.25->2	91.4/7.4
Levofloxacin	0.12	0.5	≤0.06->8	92.6/6.4
Coag. Neg. Staphylococci spp. (91)				
Meropenem	0.06	0.12	0.03-0.5	100.0/0.0
Imipenem	≤0.016	≤0.016	≤0.016-06	100.0/0.0
Aztreonam	>16	>16	>16	-/-
Ceftriaxone	1	4	≤0.25-16	98.9/0.0
Ceftazidime	4	8	1-16	94.5/0.0
Cefepime	0.5	2	≤0.12-4	100.0/0.0
Pip/Tazo	≤1	≤1	≤1-2	100.0/0.0
Gentamicin	≤1	≤1	≤1->8	98.9/1.1
Tobramycin	≤1	≤1	≤1->8	98.9/0.0
Ciprofloxacin	≤0.25	>2	≤0.25->2	87.9/11.0
Levofloxacin	0.12	2	≤0.06->8	87.9/9.9

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

CONCLUSIONS

- Meropenem again demonstrated the broadest overall activity among tested agents and was more potent than imipenem against all Enterobacteriaceae, equal against *P. aeruginosa*, two-fold less potent against *Acinetobacter* spp., and four-fold less potent against oxacillin-susceptible staphylococci.
- The emerging high incidence of KPC carbapenemases in the *Klebsiella*, *Citrobacter*, and *Serratia* spp. isolates in some medical centers is a concern due to the spread of clones within a limited geographic region.
- Susceptibility rates for the fluoroquinolones continued to decrease for all organism groups compared to prior years' USA MYSTIC Programme data and appears to be a continuing, endemic problem.
- With the remarkable changes being detected, continued surveillance (especially within Enterobacteriaceae and non-fermentative Gram-negative bacilli) appears necessary to monitor the activity of broad-spectrum antimicrobial agents used in the empiric treatment of hospital-associated serious infections.

ACKNOWLEDGEMENTS

This study was supported by an educational/research grant from AstraZeneca Pharmaceuticals. The 2005 MYSTIC Programme sites and participants in the USA were: Arkansas Children's Hospital (T. Beavers-May/R. Jacobs); Clinical Laboratories of Hawaii (F. Pien/L. Ikei-Canter); Columbia Presbyterian Medical Center (P. Della-Latta/P. Pancholi); 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, Berkeley Regional Laboratory (J. Fusco/J. Konnig); 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 Massachusetts Medical Center (M. Mitchell); University of Texas, MD Anderson Cancer Center (K. Rolston/R. Prince); University of Utah, ARUP Laboratories, Inc. (M. Bale/A. Croft); University of Washington (A. Limaye/S. Swanzy); and Winthrop University Hospital (P. Schoch).

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