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Report from the 2005 MYSTIC Surveillance Program (USA): Influence of Antimicrobial Resistant Clusters on Overall Prevalence Patterns

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MYSTIC

Meropenem Yearly Susceptibility Test Information Collection

ABSTRACT

Background:
The MYSTIC Program is a worldwide longitudinal surveillance network of >100 medical centers (MC) actively applying carbapenems. In the USA, 15 MCs participated in 2005 by submitting up to 200 consecutive, non-duplicate clinical isolates from serious infections.

Methods:
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 broth microdilution susceptibility (S) methods with interpretative criteria. Ribotyping (RT) and PFGE were performed on 203 selected strains exhibiting multi-drug resistance (MDR) and/or identical antibiograms to determine possible clonal dissemination within and between MCs.

Results:
The carbapenems had the highest S rates (≥ 98.7% vs. ENT) and the fluoroquinolones (FQ) the lowest S rates (83.9-84.9%). 101 clonally related ENT produced 12 RT patterns within 13 MCs involving 50 *E. coli* (EC, 10.2%), 31 *K. pneumoniae* (KPN, 6.9%), and 11 *P. mirabilis* (7.5%). A single RT (243.2) was observed in 45 FQ-resistant (R) EC strains from 11 MCs. RT 497.1 was observed in 20 KPC producing KPN isolates from two centers in New York (NY). The most active agents against the *P. aeruginosa* (PSA) were piperacillin/tazobactam (91.0% S), tobramycin (TOB, 88.6% S) and MEM (87.6% S) and against *Acinetobacter* spp. (ASP) were TOB (92.0% S), imipenem (92.0% S) and MEM (85.6% S). Among ASP 3 RT patterns were observed in 24 (19.2%) strains with one RT shared by 4 MCs. PSA (24) demonstrated clonal clusters in 6 MCs (range 2-9 strains per RT).

Conclusions:
Clonally related clusters of MDR isolates significantly skewed the overall S and R rates for most antimicrobials tested in the MYSTIC Program (2005). One geographic region (NY) demonstrated high numbers of clonally related ASP and PSA, carbapenemase-producing (KPC-2 and -3) KPN, but MEM remained highly active against isolates, overall. Continued surveillance within these sites appears warranted to monitor activity of broad-spectrum agents against these evolving pathogens causing clonal nosocomial infections.

INTRODUCTION

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program is an international resistance surveillance study with greater than 100 participant sites worldwide located in Europe, North America, Latin America and Asia. The study was designed to monitor the in vitro activity of meropenem and comparator broad-spectrum antimicrobial agents against bacterial isolates from serious infections in hospitals utilizing carbapenems. Fifteen medical centers 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.

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. We report the overall effect of antimicrobial resistant clones identified on the antimicrobial susceptibility testing results from the USA MYSTIC Program isolates collected in 2005.

MATERIALS AND METHODS

Specimen collection: The MYSTIC Program utilized 15 medical centers geographically dispersed across the USA. Each center requested to submit up to 200 bacterial isolates from serious infections from quotas among Enterobacteriaceae, non-fermentative Gram-negative species, and staphylococci. All isolates were shipped to the central monitoring laboratory (JMI Laboratories) on charcoal transport swabs.
In 2005, a total of 2,910 isolates (97.0% compliance) were submitted from the medical centers (range, 115 to 230 isolates per site). 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, 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. (Table 1). Interpretation of susceptibility and resistance was based on CLSI criteria (M100-S16). Quality control was assured utilizing appropriate American Type Culture Collection (ATCC) strains with all results within CLSI published ranges.

The CLSI extended spectrum ß-lactamase (ESBL) MIC screening criteria of ≥ 2 µg/ml for ceftazidime or ceftriaxone or aztreonam were applied to *Escherichia 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.

Molecular testing: Clonality was confirmed for strains demonstrating multi-drug resistance and/or highly similar antibiograms with a step-wise algorithm including testing by an automated ribotyping system (Riboprinter™ Microbial Characterization System, Qualicon, DE, USA) followed by further epidemiologic discrimination using CHEF-DRII pulsed-field gel electrophoresis (PFGE; BioRad Laboratories, Hercules, CA, USA), when necessary.

RESULTS

- Against the Enterobacteriaceae isolates, the carbapenems demonstrated the highest overall susceptibility rate (≥ 98.7%) closely followed by cefepime (97.6%) and then piperacillin/tazobactam (92.0%; Table 1).
- Ciprofloxacin and levofloxacin continued to demonstrate the lowest susceptibility rates (83.9 – 84.9%) for the Enterobacteriaceae isolates with the indole-positive Proteae and *E. coli* demonstrating the highest resistance rates (20.4 – 36.5%) (Table 1).

Table 1. Antimicrobial activity of meropenem and 10 broad-spectrum comparator agents tested against Enterobacteriaceae isolates in the USA MYSTIC Program (2005).

Organism (no. tested)/ antimicrobial agent	MIC (µg/ml) 50%	90%	Range	All isolates % susceptible/resistant[a]	Clonal isolates removed % susceptible/resistant[a]
Enterobacteriaceae				(1,657)	(1,583)
Meropenem	0.03	0.06	≤0.016->32	98.7/1.1	99.4/0.6
Imipenem	0.12	1	0.03->32	98.9/0.5	99.5/0.3
Aztreonam	≤1	8	≤1->16	90.6/7.2	92.0/5.6
Ceftriaxone	≤0.25	8	≤0.25->32	91.2/5.2	92.6/3.8
Ceftazidime	≤0.12	8	≤0.12->16	90.4/8.4	91.7/7.1
Cefepime	≤0.12	0.5	≤0.12->16	97.6/1.4	98.5/0.9
Piperacillin/Tazobactam	2	16	≤1->128	92.0/5.0	93.2/4.0
Gentamicin	≤1	4	≤1->8	90.5/7.4	92.2/5.8
Tobramycin	≤1	4	≤1->8	90.5/6.9	92.7/4.9
Ciprofloxacin	≤0.25	>2	≤0.25->2	83.9/14.8	87.8/10.9
Levofloxacin	≤0.06	8	≤0.06->8	84.9/13.2	88.9/9.3
Citrobacter spp.				(146)	(146)
Meropenem	0.03	0.06	≤0.016-2	100.0/0.0	100.0/0.0
Imipenem	0.25	1	0.06-4	100.0/0.0	100.0/0.0
Aztreonam	≤1	>16	≤1->16	80.8/10.3	80.8/10.3
Ceftriaxone	≤0.25	32	≤0.25->32	81.5/6.8	81.5/6.8
Ceftazidime	0.25	>16	≤0.12->16	80.1/19.2	80.1/19.2
Cefepime	≤0.12	1	≤0.12-16	98.6/0.0	98.6/0.0
Piperacillin/Tazobactam	2	32	≤1->128	85.6/6.8	85.6/6.8
Gentamicin	≤1	4	≤1->8	91.8/6.2	91.8/6.2
Tobramycin	≤1	4	≤1->8	91.1/6.2	91.1/6.2
Ciprofloxacin	≤0.25	1	≤0.25->2	90.4/6.2	90.4/6.2
Levofloxacin	≤0.06	2	≤0.06->8	90.4/4.8	90.4/4.8
Enterobacter spp.				(160)	(160)
Meropenem	0.03	0.06	≤0.016-16	99.4/0.6	99.4/0.6
Imipenem	0.25	1	0.06-8	99.4/0.0	99.4/0.0
Aztreonam	≤1	>16	≤1->16	76.3/16.3	76.3/16.3
Ceftriaxone	≤0.25	>32	≤0.25->32	78.8/14.4	78.8/14.4
Ceftazidime	0.25	>16	≤0.12->16	76.3/21.9	76.3/21.9
Cefepime	≤0.12	2	≤0.12-16	96.9/0.0	96.9/0.0
Piperacillin/Tazobactam	2	64	≤1->128	83.1/7.5	83.1/7.5
Gentamicin	≤1	≤1	≤1->8	92.5/6.9	92.5/6.9
Tobramycin	≤1	2	≤1->8	91.9/8.1	91.9/8.1
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	94.4/4.4	94.4/4.4
Levofloxacin	≤0.06	0.5	≤0.06->8	96.3/3.8	96.3/3.8
Escherichia coli				(491)	(454)
Meropenem	≤0.016	0.03	≤0.016-2	100.0/0.0	100.0/0.0
Imipenem	0.12	0.12	0.03-2	100.0/0.0	100.0/0.0
Aztreonam	≤1	≤1	≤1->16	95.5/3.1 (8.4)[b]	96.0/2.4
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	94.7/2.6 (6.3)[b]	95.2/2.2
Ceftazidime	≤0.12	0.5	≤0.12->16	95.1/3.1 (7.3)[b]	95.2/2.9
Cefepime	≤0.12	0.25	≤0.12->16	98.4/1.4	98.7/1.1
Piperacillin/Tazobactam	≤1	4	≤1->128	95.3/2.4	96.0/2.4
Gentamicin	≤1	>8	≤1->8	88.8/10.2	91.9/7.0
Tobramycin	≤1	4	≤1->8	91.0/5.9	93.6/3.5
Ciprofloxacin	≤0.25	>2	≤0.25->2	78.2/21.6	84.6/15.2
Levofloxacin	≤0.06	>8	≤0.06->8	78.8/20.4	85.2/14.3

Organism (no. tested)/ antimicrobial agent	MIC (µg/ml) 50%	90%	Range	All isolates % susceptible/resistant[a]	Clonal isolates removed % susceptible/resistant[a]
Klebsiella spp.				(450)	(425)
Meropenem	0.03	0.03	≤0.016->32	96.0/3.6	98.4/1.6
Imipenem	0.12	0.25	0.03->32	96.2/1.6	98.4/0.9
Aztreonam	≤1	>16	≤1->16	85.8/13.1 (15.8)[b]	90.8/8.0
Ceftriaxone	≤0.25	16	≤0.25->32	88.7/8.2 (14.4)[b]	93.6/3.5
Ceftazidime	≤0.12	>16	≤0.12->16	87.1/12.4 (15.8)[b]	92.2/7.5
Cefepime	≤0.12	2	≤0.12->16	94.7/3.6	97.4/1.9
Piperacillin/Tazobactam	2	128	≤1->128	87.6/10.9	91.5/7.3
Gentamicin	≤1	2	≤1->8	91.3/5.8	93.9/3.5
Tobramycin	≤1	>8	≤1->8	86.9/10.7	91.5/6.1
Ciprofloxacin	≤0.25	>2	≤0.25->2	85.1/14.0	87.8/8.9
Levofloxacin	≤0.06	>8	≤0.06->8	86.2/12.4	91.3/7.3
Proteus mirabilis				(147)	(140)
Meropenem	0.06	0.06	≤0.016-0.12	100.0/0.0	100.0/0.0
Imipenem	0.5	1	0.06-2	100.0/0.0	100.0/0.0
Aztreonam	≤1	≤1	≤1	100.0/0.0 (0.0)[b]	100.0/0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/0.0 (0.0)[b]	100.0/0.0
Ceftazidime	≤0.12	≤0.12	≤0.12-0.25	100.0/0.0 (0.0)[b]	100.0/0.0
Cefepime	≤0.12	≤0.12	≤0.12-0.5	100.0/0.0	100.0/0.0
Piperacillin/Tazobactam	≤1	≤1	≤1	100.0/0.0	100.0/0.0
Gentamicin	≤1	4	≤1->8	92.5/3.4	92.9/3.6
Tobramycin	≤1	2	≤1->8	96.6/0.7	96.4/0.7
Ciprofloxacin	≤0.25	2	≤0.25->2	83.0/15.6	87.1/11.4
Levofloxacin	≤0.06	2	≤0.06->8	84.4/11.6	88.6/7.9
Indole-Positive *Proteae*				(96)	(92)
Meropenem	0.06	0.12	≤0.016-0.12	100.0/0.0	100.0/0.0
Imipenem	1	2	0.06-2	100.0/0.0	100.0/0.0
Aztreonam	≤1	≤1	≤1-8	100.0/0.0	100.0/0.0
Ceftriaxone	≤0.25	1	≤0.25-8	100.0/0.0	100.0/0.0
Ceftazidime	≤0.12	8	≤0.12->16	95.8/2.1	95.7/2.2
Cefepime	≤0.12	≤0.12	≤0.12-8	100.0/0.0	100.0/0.0
Piperacillin/Tazobactam	≤1	2	≤1-16	100.0/0.0	100.0/0.0
Gentamicin	≤1	>8	≤1->8	80.2/14.6	80.4/14.1
Tobramycin	≤1	8	≤1->8	87.5/6.3	89.1/5.4
Ciprofloxacin	≤0.25	>2	≤0.25->2	59.4/36.5	62.0/33.7
Levofloxacin	0.5	>8	≤0.06->8	60.4/33.3	63.0/30.4
Serratia spp.				(134)	(134)
Meropenem	0.03	0.06	≤0.016-32	99.3/0.7	99.3/0.7
Imipenem	0.5	1	0.12->32	99.3/0.7	99.3/0.7
Aztreonam	≤1	≤1	≤1->16	97.8/2.2	97.8/2.2
Ceftriaxone	≤0.25	0.5	≤0.25->32	95.5/1.5	95.5/1.5
Ceftazidime	≤0.12	0.25	≤0.12->16	97.8/2.2	97.8/2.2
Cefepime	≤0.12	0.25	≤0.12->16	99.3/0.7	99.3/0.7
Piperacillin/Tazobactam	≤1	4	≤1-64	97.8/0.0	97.8/0.0
Gentamicin	≤1	2	≤1->8	94.8/3.7	94.8/3.7
Tobramycin	≤1	4	≤1->8	92.5/6.0	92.5/6.0
Ciprofloxacin	≤0.25	1	≤0.25->2	96.3/1.5	96.3/1.5
Levofloxacin	0.12	1	≤0.06-8	98.5/0.7	98.5/0.7

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

- The presence of clonally related, resistant isolates of *E. coli* (n=50) were identified from 11 medical centers and these strains significantly influenced the fluoroquinolone susceptibility (+6.4%) and resistance (-6.1 – -6.4%) rates (Tables 1 and 3).
- Twenty *Klebsiella pneumoniae* isolates from two New York City medical centers were identified that produce KPC-2 serine carbapenemase and were deemed clonally related because of common ribogroup and PFGE patterns (105.491.1; KPN2A/KPN4D; Table 3). KPC carbapenemases were also identified in *Citrobacter* spp. (4 strains) and *E. coli* (2 strains) from the same medical centers. One additional isolate from a Washington state medical center of *Serratia marcescens* was confirmed with a SME-2 carbapenemase (Bush group 2f).
- Piperacillin/tazobactam had the highest susceptibility rate (91.0%) against the *P. aeruginosa* isolates (589 strains) followed by tobramycin (88.6%) and meropenem (86.6%).
- Against the *Acinetobacter* spp. isolates, only tobramycin (92.0%), imipenem (92.0%) and meropenem (85.6%) demonstrated acceptable susceptibility rates (Table 2).
- The presence of clonally related strains of *P. aeruginosa* had a lesser influence on the susceptibility and resistance rates (+2.0 to -1.7%), compared to the clonally related *Acinetobacter* spp. isolates (+7.4 to -6.7%) (Tables 2 and 3).
- Among the oxacillin-susceptible staphylococci, cefepime, imipenem, meropenem and piperacillin/tazobactam demonstrated the greatest susceptibility (100.0%), and ciprofloxacin (91.4 - 87.9%) and levofloxacin (92.6 - 87.9%) had the lowest susceptibility rates against *S. aureus* and coagulase-negative staphylococci, respectively (Data not shown).

Table 2. Antimicrobial activity of meropenem and up to nine broad-spectrum comparator agents tested against non-fermentative Gram-negative bacilli in the USA MYSTIC Program (2005).

Organism (no. tested)/ antimicrobial agent	MIC (µg/ml) 50%	90%	Range	All isolates % susceptible/resistant[a]	Clonal isolates removed % susceptible/resistant[a]
P. aeruginosa				(589)	(571)
Meropenem	0.5	8	≤0.016->32	87.6/6.8	89.3/5.8
Imipenem	1	8	0.03->32	84.4/7.3	86.9/6.0
Aztreonam	8	>16	≤1->16	74.2/12.2	75.7/10.7
Ceftazidime	2	16	0.25->16	86.9/9.8	88.4/8.4
Cefepime	4	16	0.5->16	86.9/4.8	88.4/3.9
Piperacillin/Tazobactam	4	64	≤1->128	91.0/9.0	92.1/7.9
Gentamicin	≤1	>8	≤1->8	83.9/12.1	86.2/9.6
Tobramycin	≤1	>8	≤1->8	88.6/10.4	91.1/7.9
Ciprofloxacin	≤0.25	>2	≤0.25->2	72.5/22.4	74.8/20.0
Levofloxacin	0.5	>8	≤0.06->8	69.4/22.4	71.6/20.0
Acinetobacter spp.				(125)	(108)
Meropenem	0.5	8	≤0.016->32	85.6/8.0	91.7/4.6
Imipenem	0.25	4	≤0.016-16	92.0/3.2	95.4/1.9
Ceftazidime	4	>16	0.5->16	60.8/33.6	70.4/23.1
Cefepime	4	>16	≤0.12->16	64.0/22.4	74.1/14.8
Piperacillin/Tazobactam	16	>128	≤1->128	59.2/28.8	68.5/18.5
Gentamicin	≤1	>8	≤1->8	72.0/26.4	80.6/17.6
Tobramycin	≤1	4	≤1->8	92.0/5.6	92.6/4.6
Ciprofloxacin	≤0.25	>2	≤0.25->2	60.0/40.0	69.4/30.6
Levofloxacin	0.25	>8	≤0.06->8	62.4/29.6	72.2/21.3

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

Table 3. Ribogroup and pulsed-field gel electrophoresis results for clonally related isolates identified in the USA MYSTIC Program (2005) indexed by bacterial species and participant medical centers.

Organism	Site	No. isolates	Ribogroup	PFGE[a]
Acinetobacter baumanii	02	3	105.1110.4	ACB2D,D1
	02	3	105.931.7	ACB2B1
	04	4	105.931.7	ACB4B1
	17	5	105.1110.4	ACB17A
	21	5	105.1110.4	ACB21A,A1,B
	24	2	258.294.6	NT
	26	2	105.1110.4	ACB26A
Escherichia coli	01	3	105.241.4	EC1B,1C,1D
	01	14	105.243.2	EC1A,A1,A2
	02	6	105.243.2	EC2A3,A,A4,A1
	03	2	105.243.2	EC3A
	04	2	105.1118.2	NT
	04	2	105.243.2	EC4A
	08	6	105.243.2	EC8C
	11	3	105.243.2	EC11A,A1,A2
	14	2	105.243.2	EC14A
	16	2	105.243.2	EC16A
	24	2	105.243.2	EC24A,A1
	25	2	105.243.2	EC25A
	26	4	105.243.2	EC26A,A1
Klebsiella oxytoca	20	2	258.194.7	KOX20A
Klebsiella pneumoniae	02	14	105.497.1	KPN2A1,A2,A3,A5
	02	3	105.520.4	KPN2A2,A3,A4
	04	6	105.497.1	KPN4D,D1,D2
	04	2	105.512.1	KPN4D,D2
	04	4	105.520.4	KPN4D2,D
	21	2	105.204.1	KPN21B
Proteus mirabilis	03	2	258.293.7	PM3A
	16	2	258.291.6	PM16A1,A
	20	5	258.291.6	PM20A,A1,A2
	26	2	258.293.7	PM26A
Proteus stuartii	16	5	105.1010.4	PVS16A4,A1,A3
Pseudomonas aeruginosa	01	2	258.278.1	PSA1A
	04	4	252.45.6	PSA4L
	08	4	105.566.6	PSA8A,A1,B,C
	17	2	105.1224.5	PSA17A
	23	3	105.566.6	PSA23RR1
	26	9	105.780.4	PSA26A,A1,A2,A3,A4,B,C

a. NT = not tested.

CONCLUSIONS

- The carbapenems continue to show the widest overall antimicrobial activity among the broad-spectrum agents tested in the MYSTIC Program. Meropenem was more potent than imipenem against the Enterobacteriaceae, equal against *P. aeruginosa*, and two-fold less potent against *Acinetobacter* spp. isolates.
- The presence of clonally related isolates had the greatest impact on the susceptibility and resistance rates among *Acinetobacter* spp., and *Klebsiella* spp.
- The escalating incidence of serine carbapenemases (Bush group 2f) in *Klebsiella*, *Citrobacter*, and *E. coli* isolates has emerged as a concern due to the spread of resistant clones within geographic areas.
- The overall susceptibility rates for the fluoroquinolones continued to decrease compared to prior year MYSTIC Program results even with the rate adjusted to account for the presence of clonally related strains.
- Continued surveillance within the Enterobacteriaceae species and non-fermentative Gram-negative bacilli remains critical to monitor the activity of meropenem and selected broad-spectrum antimicrobial agents used in the empiric treatment of the most serious of infections.

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