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Eight-Year Trends in Carbapenem Resistance Rates in the MYSTIC Program (USA; 1999-2006)

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

AMENDED ABSTRACT

Background: The MYSTIC Program is a global longitudinal surveillance network of >100 medical centers actively using carbapenems (CARB) that monitors the activity of meropenem (MEM) and alternative broad-spectrum agents against pathogens collected from hospitalized patients. In the USA, 15 centers submit up to 200 clinical isolates each year from serious infections.
Methods: 20,041 isolates, including 9,396 Enterobacteriaceae (ENT, 46.9%), and 4,172 non-fermentative Gram-negative bacilli (NFGNB, 20.8%) were tested between 1999 and 2006 at a central laboratory using CLSI reference broth microdilution susceptibility (S) methods (M7-A7). CLSI interpretative criteria for CARB resistance (R; ≥16 µg/ml) was applied, but lower S breakpoints were required to detect the serine carbapenemases now endemic in areas of the USA.
Results: Against ENT isolates, the CARBs demonstrated the highest S rates (99.5%). 57 ENT isolates (23 clonally related) were confirmed to have KPC carbapenemases and 15 strains had MEM MIC results in the non-R range. *Acinetobacter* spp. (ASP) had the highest CARB-R rate (13.5%) followed by *P. aeruginosa* (PSA) and other NFGNB with 7.2% R. Increased R to CARBs among ENT was observed in 2005-2006, whereas rates among ASP and PSA have remained stable.

	No. isolates at MEM MIC values					
Organism (no. tested)	≤0.5	1	2	4	8	%R[a]
ASP (614)	315	82	67	39	28	13.5
ENT (9,396)	9,308	18	15	6	5	0.5 (0.7[b])
PSA (3,102)	1,795	497	265	177	144	7.2
Other NFGNB (456)	263	45	50	35	30	7.2
All (20,041)	16,912	699	443	674	756	2.8

a. CLSI M100-S16 breakpoints applied.
b. ≥8 µg/ml breakpoint used to detect serine carbapenemases.

Conclusions: MYSTIC Program results generally demonstrated the continued high activity of the CARB class against the tested pathogen groups. Continued surveillance appears warranted to monitor possible declining rate of CARB activity among ENT, as well as alternative broad-spectrum agents (all organism groups). The presence of serine carbapenemases and non-R MIC results indicates the urgent need for CLSI re-evaluated breakpoints to optimize CARB-R detection.

INTRODUCTION

Serious infections such as bacteremia and pneumonia are frequently caused by Gram-negative bacilli which are often resistant to multiple antimicrobial agents including; aminoglycosides, cephalosporins, and fluoroquinolones. The carbapenems have been the recommended drug of choice for treating these pathogens, but resistance to the carbapenems has recently been identified, first in non-fermentative Gram-negative bacilli and then in Enterobacteriaceae. Resistance to the carbapenem class was predominately due to hyper-production of AmpC ß-lactamases, and/or loss of outer membrane proteins (OMPs), and/or over expression of efflux pumps. More recently, the presence of metallo-ß-lactamases (MBL; IMP, VIM, SPM, etc.) has been observed in *Pseudomonas aeruginosa* and Enterobacteriaceae species. Currently, the most prevalent mechanism observed in the enteric bacilli in the USA is the serine carbapenemase class including IMI, NmcA, KPC and SME types of ß-lactamases. While MßLs remain very rare in Gram-negative isolates, the increase and spread of serine carbapenemases, especially KPC-type, among Enterobacteriaceae isolates has been well documented particularly in New York City and surrounding areas.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program is a global longitudinal resistance surveillance study monitoring fifteen medical centers in the United States (USA) since 1999, and bacterial strains tested by a central laboratory design (JMI Laboratories, North Liberty, Iowa, USA) using reference broth microdilution susceptibility testing methods of the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS). These surveillance studies became necessary to help 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 over eight years of the antimicrobial susceptibility testing results from the USA MYSTIC Program isolates collected between 1999 and 2006, with emphasis on carbapenem resistance among the Enterobacteriaceae (serine carbapenemases) and non-fermentative Gram-negative bacilli (diverse mechanisms).

MATERIALS AND METHODS

Specimen Collection: Each year beginning in 2000 (only ten centers in 1999) the USA MYSTIC Program has monitored 15 medical centers geographically dispersed across the USA. Each center was requested to submit up to 200 bacterial isolates (overall compliance rate of viable strains was 93.4%; range 90.0-97.0%) from serious infections defined by specific protocol quotas among Enterobacteriaceae, non-fermentative Gram-negative species, and Gram-positive cocci. Annual modifications to the protocol species and number of strains collected were made to emphasize Gram-negative bacilli or Gram-positive cocci or anaerobic pathogen sampling. *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 April 2006, a total of 20,041 isolates were submitted from the medical centers, including Enterobacteriaceae (9,396 strains), *P. aeruginosa* (3,102 strains), *Acinetobacter* spp. (614 strains), other non-fermentative Gram-negative bacilli (456 strains), methicillin-susceptible *S. aureus* (2,451 strains), methicillin-susceptible coagulase-negative *Staphylococcus* spp. (1,229 strains), *Enterococcus* spp. (1,185 strains), ß-haemolytic streptococci (740 strains), and viridans group streptococci (201 strains) (Table 1). 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 testing was performed using commercially-prepared, validated panels (TREK Diagnostics, Cleveland, OH, USA) for all strains using Clinical and Laboratory Standards Institute (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.

A screening resistance breakpoint of ≥2 µg/ml for the carbapenems was applied to detect serine carbapenemases (Bush group 2f) producing isolates of Enterobacteriaceae. All potential serine carbapenemase producing isolates were tested using a disk approximation (DA) method with meropenem and imipenem as the substrates and clavulanic acid as the inhibitor. Isolates with a positive DA test were further tested using specific PCR primers for IMI, NmcA, KPC and SME enzymes. PCR reaction products were then sequenced and compared to known sequences for identification of specific carbapenemase types.

RESULTS

- Against all the Enterobacteriaceae isolates tested in the MYSTIC Program, meropenem was the most potent carbapenem agent with a MIC_{90} 16-fold lower than imipenem, but the overall susceptibility rates were very similar (99.4-99.5%; Table 1).
- Table 2 shows the wider distribution (≤0.03->16 µg/ml) of MIC results for meropenem and imipenem tested against the Gram-negative bacilli compared to the Gram-positive cocci in the MYSTIC Program (1999-2006). Meropenem had equal potency to imipenem (MIC_{90}, 8 µg/ml) against *P. aeruginosa* and other non-fermentative bacilli but was 2-fold less potent against *Acinetobacter* spp. isolates.
- Tobramycin demonstrated the highest overall susceptibility rate (90.8%) against the *P. aeruginosa* isolates (3,102 strains) followed by piperacillin/tazobactam (89.8%) and meropenem (88.1%). Against the *Acinetobacter* spp. isolates (614 strains) imipenem (MIC_{90}, 8 µg/ml; 87.0% S) was the most active agent followed by meropenem (MIC_{90}, 16 µg/ml; 81.9% S) and tobramycin (MIC_{90} >8 µg/ml; 81.4% S; Table 1).
- Susceptibility rates for the carbapenems against Enterobacteriaceae isolates from 1999-2004 remained stable with 99.1-99.9% (Table 3). A slight, localized increase in resistance has been observed, however, from 0.0-0.1% (2003-2004) to 2.0-2.5% (2006). This increase in resistance was due to the clonal expansion of serine carbapenemase producing isolates collected from a few medical centers, principally in the New York City area (Table 4).
- The resistance rates (trends) for the carbapenems against *P. aeruginosa*, *Acinetobacter* spp. and other non-fermentative Gram-negative bacilli have not increased significantly over the 1999-2006 interval (Table 3).
- All agents tested against methicillin-susceptible *S. aureus* and coagulase-negative staphylococci demonstrated ≥93.0% susceptibility except for ciprofloxacin (84.8-91.9%; Table 1).
- Within the USA MYSTIC Program sites, only one isolate of *P. aeruginosa* has been identified as a MßL-producer (0.03%), however, there is an escalating occurrence since 2005 of serine carbapenemase producing isolates (0.7%; KPC- and SME-types) in *Klebsiella* (45 strains), *Citrobacter* (eight strains), *Enterobacter* (five strains), *Serratia* (four strains), and *E. coli* (two strains; see Table 4).
- To detect the presence of serine carbapenemase-producing isolates a lower resistance breakpoint of ≥2 µg/ml for meropenem and imipenem (≥16 µg/ml = CLSI resistance for enterics) was applied and the disk diffusion and PCR tests confirmed the presence of KPC- and SME-producing strains in 89.1% of isolates. CLSI may need to re-evaluate the current carbapenem breakpoints to facilitate laboratories ability to detect these important mechanisms of resistance.

Table 1. Antimicrobial activity of meropenem and 8 broad-spectrum comparator agents tested against isolates in the USA MYSTIC Program (1999-2006).

	MIC (µg/ml)			% by category:[a]		
Organism/antimicrobial agent (no. tested)	50%	90%	Range	Susceptible	Intermediate	Resistant
Enterobacteriaceae (9,396)						
Meropenem	0.03	0.06	≤0.016->32	99.5	<0.1	0.5
Imipenem	0.25	1	0.03->32	99.4	0.2	0.4
Ceftriaxone	≤0.25	0.5	≤0.25->32	94.5	2.6	2.9
Ceftazidime	≤0.12	1	≤0.12->16	93.7	1.1	5.3
Cefepime	≤0.12	0.25	≤0.12->16	98.8	0.4	0.9
Piperacillin/Tazobactam	≤8	≤8	≤8->64	94.7	2.3	3.0
Gentamicin	≤4	≤4	≤4->8	93.5	1.3	5.3
Tobramycin	≤1	2	≤1->8	93.9	2.0	4.1
Ciprofloxacin	≤0.25	2	≤0.25->2	89.1	1.2	9.7
P. aeruginosa (3,102)						
Meropenem	0.5	8	≤0.016->32	88.1	4.6	7.2
Imipenem	1	8	0.03->32	85.0	6.5	8.5
Ceftriaxone	>32	>32	≤0.25->32	12.4	20.8	66.8
Ceftazidime	2	>16	≤0.12->16	84.6	4.4	11.1
Cefepime	4	16	≤0.12->16	84.9	9.2	5.9
Piperacillin/Tazobactam	≤8	>64	≤8->64	89.8	-	10.2
Gentamicin	≤4	>8	≤4->8	85.0	4.9	10.1
Tobramycin	≤1	4	≤1->8	90.8	1.1	8.2
Ciprofloxacin	≤0.25	>2	≤0.25->2	73.6	5.1	21.3
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	>64	≤8->64	60.9	13.3	25.7
Gentamicin	≤4	>8	≤4->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
S. aureus (2,451)						
Meropenem	0.12	0.12	≤0.016-2	100.0	0.0	0.0
Imipenem	0.03	0.03	≤0.016-2	100.0	0.0	0.0
Ceftriaxone	4	4	≤0.25-16	>99.9	<0.1	0.0
Ceftazidime	8	8	2->16	93.1	6.7	0.2
Cefepime	2	4	0.25-16	>99.9	<0.1	0.0
Piperacillin/Tazobactam	≤8	≤8	≤8-16	>99.9	-	<0.1
Gentamicin	≤4	≤4	≤4->8	98.2	0.1	1.7
Tobramycin	≤1	≤1	≤1->8	96.2	0.8	3.0
Ciprofloxacin	≤0.25	1	≤0.25->2	91.9	1.8	6.2
CoNS[b] (1,229)						
Meropenem	0.12	0.25	≤0.016-2	100.0	0.0	0.0
Imipenem	≤0.016	0.03	≤0.016-0.25	100.0	0.0	0.0
Ceftriaxone	2	4	≤0.25-32	99.2	0.8	0.0
Ceftazidime	4	8	≤0.12->16	93.0	6.5	0.5
Cefepime	0.5	2	≤0.12-16	>99.9	<0.1	0.0
Piperacillin/Tazobactam	≤8	≤8	≤8	100.0	0.0	0.0
Gentamicin	≤4	≤4	≤4->8	94.8	1.3	3.9
Tobramycin	≤1	2	≤1->8	94.7	1.9	3.4
Ciprofloxacin	≤0.25	>2	≤0.25->2	84.8	0.1	15.1
Enterococcus spp. (1,185)						
Meropenem	8	16	0.03->32	39.7	46.1	14.2
Imipenem	2	4	≤0.016->32	98.1	1.2	0.7
Ceftriaxone	>32	>32	0.03->32	-	-	-
Ceftazidime	>16	>16	0.25->16	-	-	-
Cefepime	>16	>16	≤0.12->16	-	-	-
Piperacillin/Tazobactam	≤8	≤8	≤8->64	-	-	-
Gentamicin HL	<500	>500	≤500->500	75.5	-	24.5
Tobramycin	>8	>8	≤1->8	-	-	-
Ciprofloxacin	1	>2	≤0.25->2	57.6	9.4	33.0
ß-haemolytic streptococci (740)						
Meropenem	0.03	0.06	≤0.016-4	99.7	-	-
Imipenem	≤0.016	≤0.016	≤0.016-1	-	-	-
Ceftriaxone	≤0.25	≤0.25	≤0.25-8	99.7	-	-
Ceftazidime	0.5	1	≤0.12->16	-	-	-
Cefepime	≤0.12	≤0.12	≤0.12-16	99.7	-	-
Piperacillin/Tazobactam	≤8	≤8	≤8-16	-	-	-
Gentamicin	8	>8	≤4->8	-	-	-
Tobramycin	>8	>8	≤1->8	-	-	-
Ciprofloxacin	0.5	1	≤0.25->2	-	-	-
viridans gr. streptococci (201)						
Meropenem	0.03	0.5	≤0.016-8	91.5	-	-
Imipenem	≤0.016	0.12	≤0.016-4	-	-	-
Ceftriaxone	≤0.25	1	≤0.25->32	92.0	3.5	4.5
Ceftazidime	1	16	≤0.12->16	-	-	-
Cefepime	≤0.12	1	≤0.12->16	91.0	5.5	3.5
Piperacillin/Tazobactam	≤8	≤8	≤8-16	-	-	-
Gentamicin	≤4	8	≤4->8	-	-	-
Tobramycin	8	>8	≤1->8	-	-	-
Ciprofloxacin	2	>2	≤0.25->2	-	-	-

a. Criteria as published by the CLSI M100-S16 (2006).
b. CoNS = coagulase negative staphylococci.

Table 2. Frequency of occurrence of MIC results for meropenem and imipenem tested against Gram-negative bacilli and Gram-positive cocci in the USA MYSTIC Program (1999-2006).

	MIC (µg/ml)									
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
Enterobacteriaceae (9,396)										
Meropenem	7,385	1,568	287	42	26	18	15	6[a]	5	44
Imipenem	13	653	3,969	1,833	1,436	892	463	85[a]	19	33
P. aeruginosa (3,102)										
Meropenem	54	125	364	564	688	497	265	177[a]	144	224
Imipenem	2	10	24	103	522	1,352	484	140[a]	201	264
Acinetobacter spp. (614)										
Meropenem	10	13	42	144	136	82	67	39[a]	28	83
Imipenem	11	20	133	189	57	56	44	24[a]	37	43
S. aureus (2,451)										
Meropenem	19	578	1,690	153	8	2	1	-[a]	-	-
Imipenem	2,316	101	21	9	1	2	1	-[a]	-	-
CoNS[b] (1,229)										
Meropenem	47	462	564	132	15	8	1	-[a]	-	-
Imipenem	1,191	28	9	1	-	-	-	-[a]	-	-
Enterococcus spp. (1,185)										
Meropenem	4	1	-	-	13	11	33	408	547	168
Imipenem	4	1	1	15	32	429	575	106	14	8
ß-haemolytic streptococci (740)										
Meropenem	474	233	30	1	-[a]	1	1	-	-	-
Imipenem	731	5		2	2[a]	-	-	-	-	-
viridans gr. streptococci (201)										
Meropenem	106	38	22	13	5[a]	5	7	4	1	-
Imipenem	144	28	10	3	2[a]	7	5	2	-	-

a. Represents CLSI (2006) breakpoint for susceptibility.
b. CoNS = coagulase-negative staphylococci

Table 3. Percent susceptible and resistance rates for Enterobacteriaceae (9,396 strains) and non-fermentative bacilli (4,172) tested in the USA MYSTIC Program (1999-2006) indexed by year.

	% susceptible / resistant by year:							
Organism group/ antimicrobial agent	1999	2000	2001	2002	2003	2004	2005	2006
Enterobacteriaceae (no. tested)	(708)	(1,048)	(1,037)	(1,131)	(1,439)	(1,865)	(1,657)	(511)
Meropenem	99.7/0.3	99.4/0.6	99.8/0.1	99.8/0.1	99.9/0.0	99.9/0.1	98.7/1.1	97.5/2.5
Imipenem	99.6/0.3	99.1/0.7	99.7/0.1	99.8/0.2	99.9/0.1	99.9/0.1	98.9/0.5	97.5/2.0
P. aeruginosa (no. tested)	(193)	(299)	(298)	(321)	(454)	(689)	(589)	(259)
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	91.9/3.9
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	84.6/5.4
Acinetobacter spp. (no. tested)	(32)	(56)	(79)	(69)	(111)	(142)	(125)	(NT)[a]
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	

a. NT=not tested as part of the protocol.

Table 4. Summary of the mechanisms of resistance associated with the 57 Enterobacteriaceae isolates with elevated MIC values (≥2 µg/ml) to meropenem and imipenem within the USA MYSTIC Program (1999-2006).

Year	Organism	No. isolates	Enzyme present
1999	*Serratia marcescens*	2	SME-1
2000	*Enterobacter cloacae*	1	KPC-3
	Klebsiella pneumoniae	5	KPC-2 (1), KPC-3 (4)
2001	*Citrobacter freundii*	1	KPC-3
	Enterobacter cloacae	1	KPC-3
	Klebsiella pneumoniae	1	KPC-2/3
2002	*Citrobacter freundii*	1	KPC-3
	Enterobacter gergoviae	1	KPC-3
	Klebsiella pneumoniae	1	KPC-3
	Serratia marcescens	1	KPC-3
2003	*Klebsiella oxytoca*	2	KPC-2
2004	*Citrobacter freundii*	1	KPC-2
	Enterobacter cloacae	1	KPC-3
	Escherichia coli	1	KPC-2
	Klebsiella pneumoniae	3	KPC-2
2005	*Citrobacter freundii*	4	KPC-3 (3), KPC-2 (1)
	Escherichia coli	1	KPC-2
	Klebsiella pneumoniae	18	KPC-2
	Serratia marcescens	1	SME-2
2006 to date	*Klebsiella pneumoniae*	10	KPC-2/3

CONCLUSIONS

- The carbapenems continued 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 other non-fermentors. However, meropenem was two-fold less potent against *Acinetobacter* spp., and four- to eight-fold less potent against the staphylococci and streptococci spp. isolates.
- Susceptibility and resistance rate trends among all Gram-negative bacilli tested in the USA MYSTIC Program have generally remained stable from 1999-2006 except for a very recent decrease in carbapenem susceptibility (2005-2006) among Enterobacteriaceae isolates; greatest increase in resistance was detected for fluoroquinolones (ciprofloxacin and levofloxacin).
- The presence of MßLs among *P. aeruginosa* and Enterobacteriaceae remains extremely rare, but there appears to be an escalating incidence of serine carbapenemases (Bush gr 2f; KPC and SME) in *Klebsiella*, *Citrobacter*, *Enterobacter*, *Serratia*, and *E. coli* isolates primarily within the New York City area.
- Continued surveillance is warranted to monitor the activity of the carbapenems and comparator broad-spectrum antimicrobial agents within the clinically important Gram-negative bacilli.

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