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RESULTS FROM THE MEROPENEM YEARLY SUSCEPTIBILITY TEST INFORMATION COLLECTION (MYSTIC) PROGRAM: REPORT OF THE 2001 DATA FROM 15 MEDICAL CENTERS

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

ABSTRACT

Background: The MYSTIC Program is a global surveillance network of hospitals utilizing carbapenems, especially meropenem (MEM). Institutions have been monitored since 1997 (1999 in USA) using reference susceptibility methods (NCCLS) to detect emerging resistances (R) to carbapenems and other broad-spectrum agents. We report the results of the 2001 surveillance sample.

Methods: Fifteen medical centers participated in 2001, each asked to contribute 200 strains of specified pathogens common to nosocomial infections. A total of 2874 (95.8% compliance) strains were processed including: 1489 Gram-negative bacilli, 727 oxacillin-susceptible staphylococci, 285 streptococci and 292 enterococci. NCCLS broth microdilution methods (13 drugs) were used associated with molecular methods (ribotyping, PFGE) as needed for defining epidemic spread of R strains.

Results: The MEM MIC_{90} values were: 0.03 µg/mL for *Citrobacter* spp., *E. coli,* and *Klebsiella* spp.; 0.06 µg/mL for *P. mirabilis* and *Serratia* spp.; and *Enterobacter* spp. This potency was 8- to 16-fold greater than imipenem (IMP) and the MEM spectrum versus the Enterobacteriaceae was widest among all tested agents. MEM (MIC_{90}, 8 µg/mL), piperacillin/tazobactam and tobramycin were equally effective (potency/spectrum) against P. aeruginosa, and IMP was slightly more potent (MIC_{90}, 16 versus 32 µg/mL) for the *Acinetobacter* spp. strains tested. Some *Acinetobacters* were resistant to all tested agents and were epidemiologically linked (NYC). Only ciprofloxacin (CIPRO) and ceftazidime had compromised anti-staphylococcal activity (87.9-92.6% susceptible). The most potent agents against streptococci were MEM, ceftriaxone and cefepime (≥96.8% susceptible).

Conclusions: Over the three years monitored by the MYSTIC USA Program, no significant decline in activity or spectrum for carbapenems was observed. Reduced rates of susceptibility were most apparent for fluoroquinolones (increasing CIPRO-R) and ceftazidime, regardless of carbapenem use in monitored centers. Continued surveillance in these institutions appears prudent as sites of high potential R-risk.

INTRODUCTION

The importance of antimicrobial resistance among hospital and community-acquired pathogens is acknowledged worldwide. Antimicrobial resistance surveillance programs provide important information on trends in microbial pathogens isolated in different geographical regions and antimicrobial resistance patterns in hospital and community-acquired infections. Such information has the potential to guide the development of empiric approaches for the treatment of serious infections pending direction from local susceptibility tests, and may have value in the prevention and control of infection due to resistant organisms.

MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) is a global resistance surveillance program that, over time, compares the activity of meropenem, with other agents in medical centers that are actively prescribing meropenem. This is notable because susceptibility data can be interpreted in the context of known potential selective pressure. Previously reported data showed that resistance to meropenem was low and that the drug was highly potent against most clinically important Gram-positive and Gram-negative pathogens. Results from year three of the MYSTIC Program (2001) in the USA are described here.

METHODS

There were 15 participating USA medical centers in 2001, geographically dispersed across the USA (13 states) and all actively utilized meropenem for the treatment of seriously ill hospitalized patients. The 15 centers included 12 university medical centers, one Veterans Administration Medical Center, one cancer treatment center, two pediatric centers, and one cystic fibrosis reference medical center (some medical centers comprised more than one type of unit).

The study design and susceptibility testing methods used throughout the MYSTIC Program were described by Turner (2000) and will not be repeated in detail herein. Each of the USA centers submitted to the central monitoring laboratory for testing up to 100 aerobic Gram-negative and 100 Gram-positive isolates from serious infections in hospitalized patients. Organisms known to be intrinsically resistant to carbapenems (oxacillin-resistant staphylococci, *Enterococcus faecium* and *Stenotrophomonas maltophilia*) were excluded.

All isolates were sent to the central monitoring laboratory for identification confirmation and reference MIC determination. MICs for meropenem, imipenem, ceftriaxone, ceftazidime, cefepime, piperacillin/tazobactam, ciprofloxacin, gentamicin, and tobramycin were determined using the NCCLS broth microdilution method. Interpretive criteria for susceptibility and resistance for each antimicrobial agent were those recommended by the NCCLS.

Possible ESBL-producing isolates of *Escherichia coli* and *Klebsiella* spp. were defined as those strains with ceftazidime MICs of ≥2 µg/mL (NCCLS, 2002). ESBL production was confirmed by in-vitro synergy between ceftazidime and clavulanate (≥8-fold reduction in the ceftazidime MIC in the presence of clavulanate [4 µg/mL]) using Etest (AB BIODISK, Solna, Sweden).

RESULTS

- Meropenem was active against all enteric bacilli (MIC_{90}, 0.03-0.12 µg/mL; 100% susceptible) with the exception of two isolates of *Enterobacter* spp. (MICs, 8 and >32 µg/mL) from the same medical center. Upon molecular evaluation, the strains were not identical (ribotype and PFGE patterns). Imipenem was also active (MIC_{90}, 0.25-4 µg/mL) against this grouping of enteric bacilli with the exception of the cited isolates of *Enterobacter* spp. and one additional *Proteus mirabilis* (MIC, 8 µg/mL). Overall, the carbapenems were the most active antimicrobial agents and meropenem was generally 4- to 32-fold more potent than imipenem.

Table 1. Antimicrobial activity of meropenem compared to 10 other agents, tested against 1489 Gram-negative bacilli

Organism / antimicrobial agent	MIC (µg/mL) 50%	90%	Range	% susceptible/ resistant[a]
***Citrobacter* spp. (80)[b]**				
Meropenem	0.03	0.03	≤0.016-4	100.0/0.0
Imipenem	0.25	0.5	0.12-4	100.0/0.0
Ceftriaxone	0.12	0.5	0.03->32	91.3/1.2
Ceftizoxime	0.12	0.5	≤0.016->32	91.3/8.7
Ceftazidime	0.25	1	≤0.12->16	90.0/8.7
Cefepime	≤0.12	0.25	≤0.12-4	100.0/0.0
Aztreonam	≤0.12	1	≤0.12->16	90.0/8.7
Piperacillin/tazobactam	2	8	1->128	92.5/1.2
Gentamicin	≤2	≤2	≤2->8	93.8/6.2
Tobramycin	≤1	≤1	≤1->8	96.3/3.7
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	95.0/2.5
***Enterobacter* spp. (145)[c]**				
Meropenem	0.03	0.12	≤0.016->32	98.6/0.7[d]
Imipenem	0.5	1	0.12->32	98.6/0.7[d]
Ceftriaxone	0.12	>32	≤0.016->32	80.0/13.1
Ceftizoxime	0.12	>32	≤0.016->32	73.8/24.7
Ceftazidime	0.25	>16	≤0.12->32	75.9/19.3
Cefepime	≤0.12	2	≤0.12->16	96.6/0.7
Aztreonam	≤0.12	>16	≤0.12->16	75.9/20.7
Piperacillin/tazobactam	2	128	≤0.25->128	77.9/11.0
Gentamicin	≤2	≤2	≤2->8	95.2/4.8
Tobramycin	≤1	≤1	≤1->8	93.8/6.2
Ciprofloxacin	≤0.25	2	≤0.25->2	89.7/9.7
***E. coli* (306)**				
Meropenem	≤0.016	0.03	≤0.016-0.25	100.0/0.0
Imipenem	0.12	0.25	0.06-0.5	100.0/0.0
Ceftriaxone	0.03	0.12	≤0.016->32	98.0/0.7(3.3)[e]
Ceftizoxime	0.06	0.12	≤0.016->32	97.7/2.3
Ceftazidime	≤0.12	0.5	≤0.12->16	97.9/2.3(3.3)[e]
Cefepime	≤0.12	≤0.12	≤0.12->16	99.3/0.0
Aztreonam	≤0.21	0.25	≤0.12->16	97.7/1.0(3.6)[e]
Piperacillin/tazobactam	1	2	≤0.25->128	97.7/1.3
Gentamicin	≤2	≤2	≤2->8	95.1/4.9
Tobramycin	≤1	2	≤1->8	95.8/4.2
Ciprofloxacin	≤0.25	0.5	≤0.25->2	90.5/9.2
***Klebsiella* spp. (225)**				
Meropenem	0.03	0.03	≤0.016-4	100.0/0.0
Imipenem	0.12	0.25	0.06-4	100.0/0.0
Ceftriaxone	0.06	0.12	≤0.016->32	96.9/1.8(5.8)[e]
Ceftizoxime	≤0.016	0.12	≤0.016->32	97.3/2.7
Ceftazidime	≤0.12	1	≤0.12->16	93.8/5.3(7.1)[e]
Cefepime	≤0.12	0.25	≤0.12->16	98.7/0.7
Aztreonam	≤0.12	0.25	≤0.12->16	94.2/4.9(6.7)[e]
Piperacillin/tazobactam	2	8	≤0.25->128	96.4/2.2
Gentamicin	≤2	≤2	≤2->8	95.6/4.4
Tobramycin	≤1	≤1	≤1->8	95.6/4.4
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	94.7/3.6
***P. mirabilis* (142)**				
Meropenem	0.06	0.06	≤0.016-1	100.0/0.0
Imipenem	1	2	0.03-8	99.3/0.0
Ceftriaxone	≤0.016	≤0.016	≤0.016-8	100.0/0.0(1.4)[e]
Ceftizoxime	≤0.016	≤0.016	≤0.016->32	99.3/0.7
Ceftazidime	≤0.12	≤0.12	≤0.12->16	98.6/1.4(2.1)[e]
Cefepime	≤0.12	≤0.12	≤0.12->16	99.3/0.0
Aztreonam	≤0.12	≤0.12	≤0.12->16	98.6/1.4(1.4)[e]
Piperacillin/tazobactam	≤0.25	0.5	≤0.25-64	99.3/0.0
Gentamicin	≤2	≤2	≤2->8	93.7/6.3
Tobramycin	≤1	2	≤1->8	94.4/5.6
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	92.3/7.0
***Serratia* spp. (74)[f]**				
Meropenem	0.06	0.06	0.03-1	100.0/0.0
Imipenem	1	1	0.25-4	100.0/0.0
Ceftriaxone	0.25	1	0.06->32	98.6/1.4
Ceftizoxime	0.12	1	0.03->32	98.6/1.4
Ceftazidime	0.25	0.5	≤0.12->16	97.3/1.4
Cefepime	≤0.12	0.5	≤0.12->16	98.6/0.0
Aztreonam	≤0.12	1	≤0.12->16	97.3/2.7
Piperacillin/tazobactam	2	16	1-64	94.6/0.0
Gentamicin	≤2	≤2	≤2->8	93.2/6.8
Tobramycin	2	4	≤1->8	91.9/8.1
Ciprofloxacin	≤0.25	2	≤0.25->2	89.2/8.1
***Acinetobacter* spp. (79)**				
Meropenem	1	32	≤0.016->32	81.0/19.0
Imipenem	0.25	16	≤0.016->32	83.5/11.4
Ceftriaxone	16	>32	0.12->32	25.3/32.9
Ceftizoxime	16	>32	0.25->32	36.7/38.0
Ceftazidime	8	>16	0.5->16	64.6/29.1
Cefepime	8	>16	≤0.12->16	51.9/26.6
Aztreonam	>16	>16	4->16	12.7/78.5
Piperacillin/tazobactam	8	>128	≤0.25->128	70.9/21.5
Gentamicin	≤2	>8	≤2->8	62.0/38.0
Tobramycin	≤1	>8	≤1->8	73.4/26.6
Ciprofloxacin	≤0.25	>2	≤0.25->2	59.5/38.0
***P. aeruginosa* (298)**				
Meropenem	1	8	≤0.016->32	85.9/8.4
Imipenem	1	8	0.06->32	85.6/9.7
Ceftriaxone	>32	>32	0.25->32	10.1/68.5
Ceftizoxime	>32	>32	0.25->32	4.4/93.3
Ceftazidime	2	>16	≤0.12->16	85.6/10.1
Cefepime	4	16	0.25->16	84.2/5.4
Aztreonam	8	>16	≤0.12->16	65.1/21.5
Piperacillin/tazobactam	8	64	≤0.25->128	90.9/9.1
Gentamicin	≤2	>8	≤2->8	82.2/17.8
Tobramycin	≤1	4	≤1->8	90.0/9.1
Ciprofloxacin	≤0.25	>2	≤0.25->2	74.8/22.1

[a] Criteria as published by the NCCLS (2002).
[b] Includes *C. amalonaticus* (two strains), *C. freundii* (49 strains), *C. koseri* (24 strains), *C. braaki* (one strain), and *Citrobacter* spp. (four strains).
[c] Includes *E. aerogenes* (45 strains), *E. gergoviae* (one strain), *E. cloacae* (91 strains), *E. asburiae* (two strains), *E. cancerogenus* (one strain), *E. intermedium* (one strain), and *Enterobacter* spp. (two strains).
[d] Two strains were non-susceptible from the same medical center in New York.
[e] Percentage of ESBL phenotypes using the NCCLS (2002) screening concentration of ≥2 µg/mL.
[f] Includes *S. rubideae* (one strain), *S. marcescens* (65 strains), and *Serratia* spp. (eight strains).

Table 2. Antimicrobial activity of meropenem compared to 10 other agents, tested against oxacillin-susceptible staphylococci, streptococci and enterococci (1304 strains)

Organism / antimicrobial agent	MIC (µg/mL) 50%	90%	Range	% susceptible/ resistant[a]
***S. aureus* (453)**				
Meropenem	0.12	0.12	≤0.016-0.25	100.0/0.0
Imipenem	0.03	0.03	≤0.016-0.25	100.0/0.0
Ceftriaxone	4	4	0.5-8	100.0/0.0
Ceftizoxime	8	8	0.12->32	94.5/0.7
Ceftazidime	8	8	2-16	94.3/0.0
Cefepime	2	4	0.5-8	100.0/0.0
Aztreonam	>16	>16	≤0.12->16	0.2/99.8
Piperacillin/tazobactam	1	2	≤0.25-8	100.0/0.0
Gentamicin	≤2	≤2	≤2->8	98.9/1.1
Tobramycin	≤1	≤1	≤1->8	98.0/2.0
Ciprofloxacin	≤0.25	1	≤0.25->2	90.5/6.6
CoNs (274)[b]				
Meropenem	0.12	0.25	≤0.016-1	100.0/0.0
Imipenem	≤0.016	0.03	≤0.016-0.06	100.0/0.0
Ceftriaxone	2	4	0.03-32	98.5/1.4
Ceftizoxime	0.5	2	≤0.03->32	98.2/1.8
Ceftazidime	4	16	0.5-16	89.8/0.0
Cefepime	0.5	2	≤0.12-4	100.0/0.0
Aztreonam	>16	>16	>16	0.0/100.0
Piperacillin/tazobactam	≤0.25	1	≤0.25-2	100.0/0.0
Gentamicin	≤2	≤2	≤2->8	94.9/5.1
Tobramycin	≤1	2	≤1->8	93.8/6.2
Ciprofloxacin	≤0.25	>2	≤0.25->2	83.2/16.8
Streptococci (285)[c]				
Meropenem	0.03	0.5	≤0.016-8	89.8/2.5(97.5/-)
Imipenem	≤0.016	0.12	≤0.016-2	91.9/1.4(-/-)
Ceftriaxone	0.06	0.5	≤0.016->32	96.8/0.7 (96.8/0.7)
Ceftizoxime	0.25	16	≤0.016->32	-/-
Ceftazidime	0.5	8	≤0.12->16	-/-
Cefepime	≤0.12	0.5	≤0.12->16	97.5/0.7 (97.5/0.7)
Aztreonam	>16	>16	16->16	-/-
Piperacillin/tazobactam	≤0.25	2	≤0.25-16	-/-
Ciprofloxacin	1	2	≤0.25->2	-/-
***Enterococci* (292)**				
Meropenem	8	16	0.03->32	33.9/14.4
Imipenem	2	2	≤0.016->32	99.0/0.3
Ceftriaxone[d]	>32	>32	0.03->32	3.1/94.2
Ceftizoxime[d]	>32	>32	0.06->32	2.7/96.6
Ceftazidime[d]	>16	>16	0.25->16	1.0/99.0
Cefepime[d]	>16	>16	≤0.12->16	2.4/93.8
Aztreonam[d]	>16	>16	>16	0.0/100.0
Piperacillin/tazobactam	4	8	≤0.25-128	97.9/2.1[b]
Ciprofloxacin	1	>2	≤0.25->2	61.3/29.1
Gentamicin (HL)	≤500	>500	≤500->500	78.1/21.9

[a] Criteria as published by the NCCLS (2002).
[b] CoNS = coagulase-negative staphylococci.
[c] Includes β-haemolytic *Streptococcus* spp. (135 strains), viridans group streptococci (49 strains), *S. bovis* (three strains), and *S. pneumoniae* (98 strains). Criteria as published by the NCCLS (2002). Percent susceptible and resistant values show both *S. pneumoniae* and other *Streptococcus* spp. (in parentheses) MIC breakpoint criteria: - = no interpretive criteria found in NCCLS documents.
[d] A susceptible breakpoint of ≤8 µg/mL was used for comparison purposes.

- Meropenem was slightly more active than imipenem against *P. aeruginosa* (Table 1). Among the aminoglycosides, tobramycin was more active than gentamicin. The anti-pseudomonal cephalosporins and penicillin/β-lactamase inhibitor combinations also had 84.2 to 90.6% of isolates in the susceptible category. Ciprofloxacin, aztreonam and 'third-generation' cephalosporins were the **least active**.
- The carbapenems were the most potent agents against *Acinetobacter* spp. and tobramycin was also active (73.4% susceptible) against these strains (Table 1).

Table 3. Comparative activities of MYSTIC USA core drugs indexed by four organism groups

Antimicrobial agent	% susceptible/resistant[a] (no. tested) Gram-negative bacilli (1489)	Staphylococci (727)	Streptococci (285)	Enterococci (292)
Meropenem	95.4/3.1	100.0/0.0	89.8/2.5 (97.5/-)[b]	33.9/14.4
Imipenem	95.6/3.0	100.0/0.0	91.9/1.4 (-/-)[b]	99.0/0.3
Ceftizoxime	71.0/26.6	95.9/1.1	-	2.7/96.6
Ceftriaxone	72.5/18.3	99.4/0.0	96.8/0.7 (96.8/0.7)[b]	3.1/94.2
Ceftazidime	88.7/8.0	92.6/0.0	-	1.0/99.0
Cefepime	92.2/3.3	100.0/0.0	97.5/0.7 (97.5/0.7)[b]	2.4/93.8
Aztreonam	79.7/16.1	0.1/99.9	-	0.0/100.0
Piperacillin/ tazobactam	89.9/4.8	100.0/0.0	-	97.9/2.1
Gentamicin	89.0/11.0	97.4/2.6	-	78.1/21.9[c]
Tobramycin	91.5/8.5	96.4/3.6	-	-
Ciprofloxacin	85.3/12.6	87.8/10.5	-	61.3/29.1

[a] Categories of susceptibility assigned by NCCLS (2002) criteria.
[b] Criteria for *S. pneumoniae* with the breakpoints for other streptococci listed in parentheses.
[c] High-level resistance screen to determine potential for synergy with cell-wall active agents.

- All β-lactam antimicrobials (except aztreonam) were active against the oxacillin-susceptible isolates of staphylococci, but reduced potency was again noted for ceftazidime and ceftizoxime; each had isolates with intermediate or resistant MICs (Tables 2 and 3). Aminoglycosides and ciprofloxacin were also active, however, the fluoroquinolone resistance increased to a 6.6-16.8% level.
- The activity against other Gram-positive species was comparable among all drugs with the carbapenems, cefepime and gentamicin being most potent overall (Tables 2 and 3). Ciprofloxacin was only 50% active among this group of organisms. Against streptococci, the usable agents (carbapenems, ceftriaxone and cefepime) were similar in overall activity. Against enterococci, imipenem and piperacillin/tazobactam were active against over 95% of the organisms tested.
- Table 3 summarizes the activity of the MYSTIC core antimicrobials versus the four groups of bacteria tested. The carbapenems, piperacillin/tazobactam, and cefepime had the widest range or coverage of the agents tested in the 2001 MYSTIC USA Program.

CONCLUSIONS

- **In year three (2001) of the MYSTIC USA Program, no significant decline in the activity or spectrum for meropenem was observed, confirming the experience of the previous year.**
- **Reduced susceptibilities were, however, noted for ciprofloxacin and ceftazidime.**
- **Resistance to carbapenems, when observed, appears to be rare, clonal, sporadic and unsustained.**

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