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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

# MEROPENEM YEARLY SUSCEPTIBILITY TEST INFORMATION COLLECTION (MYSTIC) PROGRAM, USA: TRENDS IN RESISTANCE, MOLECULAR EPIDEMIOLOGY AND ANTIMICROBIAL USAGE

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## INTRODUCTION

Antimicrobial resistance surveillance programs provide useful information regarding trends in microbial pathogen distribution and antimicrobial resistance patterns in nosocomial and community-acquired infections.[1] Such information has the potential to help in the development of empiric treatment protocols and may have value in the prevention and control of infection due to resistant organisms.[2]

MYSTIC is a global resistance surveillance program that compares the in-vitro activity of meropenem over time with 8 other widely used antimicrobials in medical centers that are actively prescribing meropenem (MEM).[3] Results from the first 2 years of the MYSTIC Program (1999 and 2000) in the USA are described here. Resistant pathogens clustered in time and locations are characterized by molecular epidemiologic typing methods, and patterns of antimicrobial usage in selected medical centers, are also examined.

## METHODS

- Each center submitted up to 100 aerobic Gram-negative and 100 Gram-positive isolates (Table 1). The few organisms known to be inherently resistant to carbapenems (oxacillin-resistant staphylococci, Enterococcus faecium, and Stenotrophomonas maltophilia) were excluded
- MICs for MEM, imipenem (IPM), ceftriaxone (CTX), ceftazidime (CAZ), cefepime (CPE), piperacillin/tazobactam (TAZ), ciprofloxacin (CIP), gentamicin (GM), and tobramycin (TM) were determined using the NCCLS broth microdilution method[4] and susceptibilities were determined using NCCLS interpretive criteria[5]
- Isolates from USA centers were sent to a central laboratory (Jones Microbiology Institute [JMI], North Liberty, IA) for identification confirmation and reference MIC determination
- Extended spectrum β-lactamase (ESBL)-producing isolates of Escherichia coli and Klebsiella pneumoniae were defined as those with CAZ MICs of ≥2 mg/L. ESBL production was confirmed by in-vitro synergy between CAZ and clavulanate (>4-fold reduction in the CAZ MIC in the presence of clavulanate)
- Organisms with similar resistant antimicrobial phenotypes that were also linked in time, and were from the same center, were characterized further using ribotyping and pulsed-field gel electrophoresis

## RESULTS

- 4488 significant pathogens (Table 1) were obtained in 1999 (1800 isolates; 10 centers) and 2000 (2688 isolates, 15 centers) from study centers in the USA

### Gram-negative bacilli (Table 2)

- MEM was the most active (94% susceptible) and CTX was the least active (69%) agent tested against the Gram-negative pathogens
- The overall antimicrobial rank order was the same for both study periods: MEM = TM (94%) > IPM (93%) > CPE = GM (92%) > TAZ (91%) > CAZ (90%) > CIP (89%) > CTX (69%)
- Some differences in activity were seen between the carbapenems (Table 2). MEM was seen to have lower MICs than IPM for E. coli, Klebsiella spp., Enterobacter spp., Citrobacter spp., Serratia spp. and Pseudomonas aeruginosa
- A decrease in overall Gram-negative coverage was observed for CIP (91% susceptible in 1999 and 88% in 2000). The greatest decline in the activity of CIP was observed with Acinetobacter spp. (72-63%) and P. aeruginosa (83-74%)
- The activity of CTX against Acinetobacter spp. was already low in 1999 (34% susceptibility) and this declined even further in 2000 to 25% susceptibility
- There was a decrease in the activity of CAZ versus Citrobacter spp.: 85% susceptibility in 1999 and 75% susceptibility in 2000
- The activity of TAZ against Acinetobacter spp. declined significantly between 1999 (72%) and 2000 (59%), as did its activity against Citrobacter spp. (98% in 1999 and 88% in 2000)

### Gram-positive cocci (data not shown)

- MEM was highly active against staphylococci (100% susceptible) and Streptococcus pneumoniae (95%)
- None of the agents tested was particularly active against the enterococci as defined by NCCLS breakpoint criteria

### ESBL and other resistance mechanisms

- Strains producing ESBLs and/or stably derepressed AmpC β-lactamases were uncommon and were observed in only a few centers
- ESBL rates for E. coli declined slightly from 3-5% in 1999 to 2-3% in 2000 and ESBL rates for Klebsiella spp. were stable at 6-7%
- MEM was active against 98-100% of ESBL-producing strains

### Molecular typing (Table 3)

Clonal outbreaks of resistant Gram-negative species were observed in some MYSTIC centers:

- Resistance to CIP was noted among E. cloacae clustered in 1 institution with a significant increase in utilization of CIP, 3rd-generation cephalosporins, CPE and carbapenems relative to 1999. A single isolate of E. cloacae was noted to be resistant to carbapenems, CPE and CIP
- A cluster of K. pneumoniae isolates resistant to CAZ, CPE and carbapenems was observed in 1 institution; 4 of the 5 isolates were the same strain
- A small sporadic cluster of S. marcescens was detected in 1999 with carbapenem resistance due to expression of SME-1 carbapenemase. None have been detected in 2000
- Clonal spread of Citrobacter freundii resistant to CAZ and aztreonam was observed in 2 different centers with high utilization of all antimicrobial classes
- Three different clusters of carbapenem-resistant A. baumannii were seen in 3 different institutions. The epidemic strain was the same in all three clusters and occurred within the same metropolitan area
- Clusters of resistant organisms usually represented clonal spread within institutions with high antimicrobial utilization

Table 1. Aerobic bacteria tested in the MYSTIC USA antimicrobial surveillance program, 1999 and 2000

| Organism | No. of Isolates 1999 | 2000 |
|---|---|---|
| Staphylococci | 406 | 699 |
| Streptococci | 180 | 242 |
| Enterococci | 222 | 281 |
| Other Gram-positive cocci | 35 | 24 |
| **Enteric bacilli** | **711** | **1044** |
| Citrobacter spp. | 46 | 68 |
| Escherichia coli | 197 | 313 |
| Enterobacter spp. | 100 | 158 |
| Klebsiella spp. | 152 | 233 |
| Proteus mirabilis | 95 | 143 |
| Serratia spp. | 53 | 74 |
| Other | 68 | 55 |
| **Non-fermentative Gram-negative bacilli** | **246** | **398** |
| Pseudomonas aeruginosa | 193 | 299 |
| Acinetobacter spp. | 32 | 56 |
| Other | 21 | 43 |
| **Total** | **1800** | **268** |

Table 2. Activity of MEM and comparators against selected Gram-negative pathogens from MYSTIC USA, 1999 and 2000

| Organism | Antimicrobial | 1999 $MIC_{50/90}$ | 1999 %S[a] | 2000 $MIC_{50/90}$ | 2000 %S[a] |
|---|---|---|---|---|---|
| E. coli | MEM | 0.03/0.03 | 100 | 0.016/0.03 | 100 |
| | IPM | 0.25/0.5 | 100 | 0.12/0.5 | 100 |
| | CTX | 0.06/0.12 | 98 | 0.03/0.12 | 99 |
| | CAZ | 0.12/0.5 | 97 | 0.12/0.5 | 98 |
| | CPE | 0.12/0.12 | 99 | 0.12/0.12 | 99 |
| | TAZ | 2/4 | 98 | 1/4 | 98 |
| | CIP | 0.25/0.25 | 96 | 0.25/0.25 | 97 |
| | GM | 2/2 | 96 | 2/2 | 98 |
| | TM | 1/2 | 96 | 1/1 | 97 |
| Klebsiella spp. | MEM | 0.03/0.06 | 100 | 0.03/0.06 | 98 |
| | IPM | 0.5/1 | 100 | 0.25/1 | 98 |
| | CTX | 0.06/0.12 | 97 | 0.06/0.12 | 96 |
| | CAZ | 0.25/0.5 | 96 | 0.25/0.5 | 94 |
| | CPE | 0.12/0.5 | 100 | 0.12/0.25 | 97 |
| | TAZ | 4/8 | 93 | 2/8 | 96 |
| | CIP | 0.25/0.5 | 95 | 0.25/0.25 | 94 |
| | GM | 2/2 | 96 | 2/2 | 95 |
| | TM | 1/1 | 95 | 1/1 | 95 |
| Enterobacter spp. | MEM | 0.06/0.25 | 99 | 0.03/0.12 | 99 |
| | IPM | 1/2 | 100 | 0.5/1 | 99 |
| | CTX | 0.25/32 | 83 | 0.25/32 | 86 |
| | CAZ | 0. 5/>16 | 81 | 0.25/>16 | 84 |
| | CPE | 0.12/1 | 97 | 0.12/0. 5 | 99 |
| | TAZ | 2/64 | 86 | 2/32 | 88 |
| | CIP | 0.25/0.25 | 98 | 0.25/0.25 | 98 |
| | GM | 2/2 | 98 | 2/2 | 98 |
| | TM | 1/1 | 99 | 1/1 | 98 |
| Citrobacter spp. | MEM | 0.03/0.06 | 100 | 0.03/0.06 | 100 |
| | IPM | 0.25/1 | 100 | 0.5/1 | 100 |
| | CTX | 0.25/16 | 85 | 0.12/32 | 79 |
| | CAZ | 0.5/16 | 85 | 0.25/>16 | 75 |
| | CPE | 0.12/0.5 | 98 | 0.12/2 | 100 |
| | TAZ | 2/16 | 98 | 2/128 | 88 |
| | CIP | 0.25/0.5 | 94 | 0.25/1 | 96 |
| | GM | 2/2 | 98 | 2/2 | 93 |
| | TM | 1/1 | 98 | 1/4 | 91 |
| Serratia spp. | MEM | 0.06/0.12 | 96 | 0.06/0.12 | 100 |
| | IPM | 2/2 | 96 | 1/2 | 100 |
| | CTX | 0.25/2 | 98 | 0.25/4 | 95 |
| | CAZ | 0.25/1 | 100 | 0.25/1 | 96 |
| | CPE | 0.12/0.5 | 100 | 0.12/0.25 | 99 |
| | TAZ | 2/4 | 98 | 2/8 | 96 |
| | CIP | 0.25/1 | 93 | 0.25/1 | 91 |
| | GM | 2/2 | 98 | 2/2 | 96 |
| | TM | 2/4 | 94 | 1/4 | 92 |
| Acinetobacter spp. | MEM | 0.5/32 | 78 | 1/32 | 79 |
| | IPM | 0.25/8 | 81 | 0.25/16 | 80 |
| | CTX | 16/>64 | 34 | 16/>64 | 25 |
| | CAZ | 4/>16 | 69 | 4/>16 | 66 |
| | CPE | 4/>16 | 69 | 4/>16 | 61 |
| | TAZ | 2/>128 | 72 | 16/>128 | 59 |
| | CIP | 0.5/>2 | 72 | 0.25/>2 | 63 |
| | GM | 2/>8 | 66 | 2/>8 | 64 |
| | TM | 1/>8 | 72 | 1/>8 | 79 |
| P. aeruginosa | MEM | 1/16 | 78 | 0.5/8 | 84 |
| | IPM | 2/16 | 78 | 2/16 | 81 |
| | CTX | 64/64 | 5 | 64/64 | 9 |
| | CAZ | 4/>16 | 83 | 4/>16 | 83 |
| | CPE | 4/16 | 79 | 4/16 | 81 |
| | TAZ | 8/>128 | 89 | 8/128 | 86 |
| | CIP | 0.25/>2 | 83 | 0.25/>2 | 74 |
| | GM | 2/8 | 87 | 2/8 | 82 |
| | TM | 1/2 | 93 | 1/2 | 92 |

[a] Percent susceptible determined using NCCLS interpretive criteria[5]

Table 3. Molecular analysis of organism clusters exhibiting resistance patterns from MYSTIC USA, 1999 and 2000

| Center # | Isolate # | Species | Ribotype | Comments |
|---|---|---|---|---|
| **2** | **Cluster of *E. cloacae* infections in center with increased usage of carbapenems, CPE and fluoroquinolones** | | | |
| | 11 | E. cloacae | 1755.4 | Isolates 11 and 64 are resistant to fluoroquinolones |
| | 64 | E. cloacae | 1755.4 | |
| | 29 | E. cloacae | 1755.5 | Isolate 29 is resistant to carbapenems and CPE |
| | 50 | E. cloacae | 1755.6 | Isolates 50 and 52 are AmpC hyperproducers |
| | 52 | E. cloacae | 512.3 | |
| **6** | **Cluster of *K. pneumoniae* resistant to carbapenems, CPE and 3rd-generation cephalosporins in institution with history of ESBLs and heavy usage of carbapenems** | | | |
| | 296 | K. pneumoniae | 1752.5 | |
| | 286 | K. pneumoniae | 204.2 | Clonal spread of RT 204.2 |
| | 297 | K. pneumoniae | 204.2 | |
| | 796 | K. pneumoniae | 204.2 | |
| | 440 | K. pneumoniae | 204.2 | |
| **13** | **Cluster of carbapenem resistance (SME-1 carbapenemase)** | | | |
| | 1775 | S. marcescens | 1754.7 | |
| | 1776 | S. marcescens | 635.2 | S. marcescens RT 635.2 in 1999. None in 2000 despite high carbapenem usage |
| | 1772 | S. marcescens | 635.2 | |
| **6** | **Cluster of *C. freundii* resistant to 3rd-generation cephalosporins and aztreonam (AmpC)** | | | |
| | 454 | C. freundii | 1752.1 | Clonal spread of RT 1752.1 |
| | 449 | C. freundii | 1752.1 | |
| | 453 | C. freundii | 1752.1 | |
| | 418 | C. freundii | 151.7 | |
| **4** | **CAZ and aztreonam resistant cluster** | | | |
| | 594 | C. freundii | 151.1 | |
| | 529 | C. freundii | 151.1 | |
| **2** | | | | |
| | 59 | A. baumannii | 393.6 | Cluster resistant to both MEM and IPM (RT 393.6) |
| | 51 | A. baumannii | 393.6 | |
| | 107 | A. baumannii | 393.6 | |
| | 63 | A. baumannii | 150.3 | Isolate 63 resistant to MEM but not IPM |
| **4** | | | | |
| | 522 | A. baumannii | 393.6 | Isolates 522 and 825 resistant to both MEM and IPM |
| | 825 | A. baumannii | 393.6 | |
| | 575 | A. baumannii | 150.6 | Isolate 575; MIC 8 mg/L for both MEM and IPM |
| **6** | **Cluster resistant to both MEM and IPM** | | | |
| | 292 | A. baumannii | 393.6 | |
| | 294 | A. baumannii | 393.6 | |
| | 295 | A. baumannii | 393.6 | |
| | 299 | A. baumannii | 393.6 | |
| **7** | ***P. aeruginosa* resistant to aminoglycosides and fluoroquinolones, not clonal** | | | |
| | 2345 | P. aeruginosa | 1766.1 | |
| | 2354 | P. aeruginosa | 1766.2 | |
| | 2417 | P. aeruginosa | 1766.3 | |

## CONCLUSIONS

- **Results for 1999 and 2000 from the MYSTIC USA surveillance program show a pattern of sustained potency and spectrum for the carbapenems and decreased activity of CPE, 3rd-generation cephalosporins, aminoglycosides and fluoroquinolones in specific, high antimicrobial usage institutions**
- **Antimicrobial resistance among the Gram-negative pathogens was largely confined to institutions with clonal outbreaks**
- **These observations stress the need for both formulary control and good infection control practices**
- **MEM retained the widest spectrum of activity among the β-lactams against Gram-negative and Gram-positive pathogens**

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