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CARBAPENEM RESISTANCE IN ENTERIC BACILLI AND *PSEUDOMONAS AERUGINOSA* IN THE USA (1999-2002): REPORT FROM THE MYSTIC PROGRAM

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

INTRODUCTION

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program was initiated, internationally in 1997 and commenced surveillance in North America in 1999. Currently, more than 100 different medical centers, representing over 30 countries throughout Europe, North America, Latin America, and the Asia-Pacific regions participate.

MYSTIC is a global longitudinal antimicrobial resistance surveillance program involving medical centers utilizing meropenem. In the program, the in-vitro activity of meropenem against bacterial isolates is compared with the activity of several other broad-spectrum antimicrobial agents. Several unique characteristics of the MYSTIC Program include: 1) the monitoring of clinical isolates collected from centers that use broad-spectrum antimicrobials extensively; 2) it allows correlations between microbiology data and antimicrobial usage to be determined; and 3) it enables direct comparisons to be made between specialist units (intensive care, cystic fibrosis, neutropenia, and general wards) nationally and internationally that treat high-risk patients.

Information gathered from this type of surveillance program can help guide empiric therapy of serious infections, and has added value in the prevention and control of resistant organisms via focused interventions.

The purpose of this report is to provide 4 years of MYSTIC data focusing on susceptibility and resistance patterns of enteric bacilli and *Pseudomonas aeruginosa* within medical centers in North America.

METHODS

The 15 participating medical centers were geographically dispersed across the United States (US) and all actively utilized meropenem for the treatment of seriously ill hospitalized patients. The current centers include 14 university medical centers, 1 Veterans' Administration Medical Center, 1 cancer treatment center, 2 pediatric centers, and 1 cystic fibrosis reference center (some medical centers comprised more than one type of patient population).

Once a year, each participant in the US submitted 100 Gram-negative and 100 Gram-positive isolates to a central processing laboratory. Organisms known to be intrinsically resistant to carbapenems (oxacillin-resistant staphylococci, *Stenotrophomonas maltophilia* and *Enterococcus faecium*) were excluded.

Isolates were tested for susceptibility to the antimicrobial agents on validated dry-form broth microdilution reference MIC panels. NCCLS susceptibility methods and interpretive criteria were utilized. Possible ESBL-producing isolates of *Escherichia coli* and *Klebsiella* spp. were defined as 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 MIC in the presence of clavulanate).

To determine the epidemiological significance of observed carbapenem-resistant isolates, both riboprinting and/or pulsed-field gel electrophoresis (PFGE) were performed.

RESULTS

- Meropenem (99.7% % susceptible [S]) and imipenem (99.6% S) had nearly complete activity against enteric bacilli. Rank order for lowest resistance (R) rates was: meropenem = imipenem (0.3%) > cefepime (0.5%) > ceftriaxone (2.3%) > piperacillin/tazobactam (2.5%) > tobramycin (3.1%) > gentamicin (3.8%) > aztreonam (4.4%) > ceftazidime (4.8%) > ceftizoxime = ciprofloxacin (5.6%) (Table 1).
- Against the non-fermentative Gram-negative bacilli (mostly *P. aeruginosa*), cefepime (77.4% S; 11.2% R), imipenem (82.9% S; 11.7% R), meropenem (84.5% S; 10.9% R), and piperacillin/tazobactam (88.1% S; 11.9% R) were the most active and had the broadest spectrum of activity of the agents tested. Ciprofloxacin, aztreonam, ceftriaxone, and ceftizoxime offered little clinical utility due to their high resistance rates (Table 1).

Table 1. Comparative activities of MYSTIC (USA) antimicrobials indexed for enteric and non-fermentative Gram-negative bacilli (1999-2002)

	% susceptible/resistant[a] (no. tested)			
Antimicrobial agent	Enterobacteriaceae (3925)	Rank order[b]	Non-fermentative (1537)	Rank order[b]
Meropenem	99.7/0.3	1	84.5/10.9	2
Imipenem	99.6/0.3	2	82.9/11.7	4
Ceftizoxime	93.9/5.6	10	13.7/81.6	11
Ceftriaxone	95.3/2.3	4	17.8/58.8	10
Ceftazidime	94.1/4.8	9	81.1/13.8	5
Cefepime	99.2/0.5	3	77.4/11.2	7
Aztreonam	94.2/4.4	8	53.0/33.0	9
Piperacillin/ tazobactam	95.1/2.5	6	88.1/11.9	1
Gentamicin	95.1/3.8	7	77.5/16.7	6
Tobramycin	95.3/3.1	5	84.4/13.7	3
Ciprofloxacin	93.2/5.6	11	70.1/24.3	8

a. Categories of susceptibility assigned by NCCLS (2002) criteria.
b. Rank order determined by % susceptible only. Rank order may change when considering the % resistant results; most evident for the non-fermentors.

- During the 4 years of surveillance, 11 enteric bacilli were categorized as meropenem-resistant and imipenem-resistant (Table 2). These sporadic cases show evidence of epidemic transmissions; 2 isolates of *Serratia marcescens* from site 10 in 1999, and 4 isolates of *Klebsiella* spp. from site 6 in 2000 (Table 2).
- Of the 17 isolates that were non-susceptible to imipenem, 6 were meropenem-susceptible. These comprised 6 isolates of *Proteus mirabilis* from 5 different medical centers and 1 isolate of *Serratia marcescens* (data not shown).

Table 2. Epidemiologic clonality of the 11 meropenem-resistant isolates observed in the MYSTIC USA Program (1999-2002)

Isolate #	Site	Organism	Year	Ribotype
1065	10	*S. marcescens*	1999	191.1[a]
1066	10	*S. marcescens*	1999	191.1[a]
286	06	*K. pneumoniae*	2000	204.2[b]
297	06	*K. pneumoniae*	2000	204.2[b]
440	06	*K. pneumoniae*	2000	204.2[b]
796	06	*K. pneumoniae*	2000	204.2[b]
296	06	*K. pneumoniae*	2000	1752.5
29	02	*E. cloacae*	2000	1755.4
1465	02	*E. cloacae*	2001	107.1
1466	02	*Enterobacter aerogenes*	2001	107.2
1808	02	*Enterobacter gergoviae*	2002	107.3

a. Epidemic cluster of a SME-1 serine enzyme.
b. Epidemic cluster of an ESBL-producing strain with an associated OMP alteration.

Table 3. Activity of 11 antimicrobial agents against enteric Gram-negative bacilli in the MYSTIC USA Program (1999-2002)

	% susceptible/resistant by year:[a]			
Antimicrobial agent	1999 (n=708)	2000 (n=1049)	2001 (n=1037)	2002 (n=1131)
Meropenem	99.7/0.3	99.4/0.6	99.8/0.1	99.8/0.1
Imipenem	99.6/0.3	99.1/0.7	99.7/0.1	99.8/0.1
Ceftizoxime	94.1/5.3	93.5/5.6	94.1/5.7	NT[b]
Ceftriaxone	95.8/1.7	94.6/2.9	95.2/2.6	95.8/1.9
Ceftazidime	94.6/4.0	93.2/5.6	93.1/5.5	95.3/3.9
Cefepime	99.6/0.4	98.8/1.0	98.8/0.3	99.6/0.3
Aztreonam	94.4/3.5	93.8/5.0	93.5/5.3	95.1/3.5
Piperacillin/ tazobactam	95.6/2.3	95.4/2.6	94.3/2.5	95.1/2.6
Gentamicin	96.9/2.7	95.5/4.0	94.6/3.8	94.1/4.5[c]
Tobramycin	97.0/1.7	95.1/3.3	95.0/2.9	94.7/3.8[c]
Ciprofloxacin	95.3/3.7	94.6/4.4	92.1/6.8	91.7/6.8[c]

a. Categories of susceptibility assigned by NCCLS (2002) criteria.
b. Not tested in study year.
c. Increasing resistance trends needing continued monitoring.

- The rare carbapenem-resistant isolates were associated with sporadic clusters and subsequently disappeared.
- 4-year data showed that ESBL phenotypes were observed in 4.4% of *Klebsiella* spp. and 4.1% of *E. coli* isolates. The carbapenems retained complete coverage against these problematic isolates.
- The carbapenems demonstrated nearly 100% activity throughout the surveillance period against enteric Gram-negative bacilli. Susceptibility/resistance rates remained stable (99.1-99.8%/ 0.1-0.7%, respectively) throughout the study period (Table 3). There was increasing resistance to gentamicin, tobramycin and ciprofloxacin; this trend requires further monitoring.
- Non-fermentative Gram-negative bacilli exhibited a continuous increase in susceptibility to meropenem and imipenem (79.5-90.3%/77.9-87.4%, respectively) (Table 4). This was in contrast to stable or declining susceptibility to the other antimicrobial agents tested (Table 4).
- Ciprofloxacin showed steadily decreasing activity against both enteric and non-fermentative Gram-negative bacilli (95.3-91.7% S/79.5-66.2% S, respectively) (Tables 3 and 4).

Table 4. Activity of 11 antimicrobial agents against non-fermentative Gram-negative bacilli in the MYSTIC USA Program (1999-2002)

	% susceptible/resistant by year:[a]			
Antimicrobial agent	1999 (n=249)	2000 (n=410)	2001 (n=425)	2002 (n=435)
Meropenem	79.5/15.6	81.0/13.2	84.7/10.4	90.3/6.6[b]
Imipenem	77.9/15.6	78.3/14.7	85.4/10.1	87.4/8.4[b]
Ceftizoxime	13.7/82.7	13.7/83.9	13.6/78.9	NT[c]
Ceftriaxone	13.7/65.1	15.6/66.1	16.0/57.6	23.6/49.7
Ceftazidime	81.9/11.2	80.5/15.4	81.9/13.2	80.6/14.3
Cefepime	77.5/8.4	76.8/13.7	76.0/10.6	79.0/11.0
Aztreonam	54.6/31.7	52.0/33.2	50.8/36.9	55.2/29.8
Piperacillin/ tazobactam[d]	88.4/11.6	85.1/14.9	89.2/10.8	89.6/10.4
Gentamicin	81.9/14.5	75.9/16.6	74.6/18.8	79.2/16.1
Tobramycin	87.6/10.8	84.9/13.2	82.6/16.0	83.9/13.5
Ciprofloxacin	79.5/14.1	69.5/24.4	69.2/27.1	66.2/27.4[e]

a. Categories of susceptibility assigned by NCCLS (2002) criteria.
b. Possible trend toward decreasing resistance.
c. Not tested in study year.
d. *P. aeruginosa* breakpoint applied at ≤64 µg/ml (susceptible) and ≤128 µg/ml (resistant).
e. Possible trend toward increasing resistance.

CONCLUSIONS

- **Meropenem remains among the most effective therapeutic options for the treatment of both enteric and non-fermentative Gram-negative bacillary infections in the US.**
- **Rare carbapenem-resistant isolates were associated with sporadic epidemic clusters, which have since disappeared. 6 of the 17 imipenem-non-susceptible isolates were susceptible to meropenem.**
- **Trend analysis from 1999 through 2002 showed:**
  - **a slight increase in activity of the carbapenems against non-fermentative isolates (mainly *P. aeruginosa*)**
  - **ciprofloxacin had a significantly reduced spectrum against both enteric and non-fermentative Gram-negative bacilli**
  - **a modest decline in the aminoglycoside activity was also observed.**

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