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Comparative Antimicrobial Spectrum and Potency of Meropenem Tested Against Enterobacteriaceae and Non-Fermentative Gram-Negative Bacilli: Report from the 2004 MYSTIC Programme (USA)

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

ABSTRACT

Background: The Meropenem (MEM) Yearly Susceptibility Test Information Collection (MYSTIC) Programme is a longitudinal resistance (R) surveillance network of >100 medical centers worldwide created to monitor bacterial susceptibilities (S) to carbapenems and other broad-spectrum antimicrobial agents. In 2004, 15 medical centers in the USA participated by submitting 200 consecutive, non-duplicate Gram-negative bacterial isolates from clinical infections with target numbers of specified species or pathogen groups.

Methods: A total of 2,799 Gram-negative isolates (Enterobacteriaceae [ENT; 1,865], *Pseudomonas aeruginosa* [PSA; 689], and *Acinetobacter* spp. [ASP; 142]), were collected and tested for S using NCCLS reference methods and interpretative criteria (M100-S14; 2004). Antimicrobial agents included were carbapenems (2), cephalosporins (3), aztreonam, piperacillin/tazobactam, aminoglycosides (3), and fluoroquinolones (FQ; 2).

Results: Against the 1,865 ENT isolates, MEM and imipenem (IMP) demonstrated the greatest % S with MEM showing an eight-fold greater potency (MIC_{90}, 0.06 versus 0.5 μg/ml). All agents tested were ≥ 92.1 % S except for both FQs (86.1-86.9% S; lowest for ciprofloxacin). Carbapenems retained activity against all ENT isolates with an ESBL phenotype (confirmed and unconfirmed isolates). The FQs demonstrated much lower S rates among *E. coli* (21.0 - 21.1% R) and indole-positive *Proteus* spp. (41.1 - 43.3% R) compared to the other broad-spectrum agents tested. Against PSA strains, the most active antimicrobials, with >90% S were: amikacin (AMK), tobramycin (TOB), and MEM. For the ASP isolates AMK, TOB, IMP, and MEM were the most active agents (range 76.1 – 84.5% S).

Conclusions: These 2004 MYSTIC Programme results demonstrated the continued, superior (six years) potency and spectrum of activity for MEM against ENT (99.9% S) and PSA (90.3% S) isolates. Only the aminoglycosides and carbapenems demonstrated acceptable levels of S against ASP isolates. Ongoing surveillance within these medical centers is required to monitor increasing antimicrobial resistance rates for these most widely applied broad-spectrum compounds.

INTRODUCTION

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Programme is a longitudinal resistance surveillance study encompassing greater than 100 sites worldwide located in Europe, North America, Latin America and Asia. The program is designed to monitor the in vitro activity of meropenem and other broad-spectrum antimicrobial agents. Antimicrobial resistance surveillance studies such as the SENTRY Antimicrobial Surveillance Program, PROTEKT, SCOPE, Alexander Project and MYSTIC Programme monitor a variety of bacteriologic factors including pathogen occurrence rates, susceptibility profiles and changing drug usage trends on a local, regional and/or global level. Reports and comparisons from these studies can inform clinicians about the local endemic resistance patterns and frequency rates. These results can also be useful in choosing appropriate empiric antimicrobial therapy and to guide infection control/formulary policies.

We report the antimicrobial susceptibility testing results from the MYSTIC Programme (USA) isolates collected in 2004 and tested against meropenem and 11 other broad spectrum agents. These results demonstrate the continued excellent potency and spectrum of activity for meropenem against Gram-negative pathogens causing serious infections. Included in 2004 are the first results for amikacin tested against both Enterobacteriaceae and non-fermentative Gram-negative bacilli.

MATERIALS AND METHODS

Study Design. The MYSTIC Programme in 2004 utilized 15 medical centers geographically dispersed across the USA. Five of the original 10 medical centers recruited in 1999 continued their participation. The study protocol requested specific quotas per center among Gram-negative species up to a total of 200 isolates originating from serious infections. Only *Stenotrophomonas maltophilia* and *Chryseobacterium* spp. were excluded from collection due to their intrinsic, enzyme-mediated resistances to carbapenems. All isolates were submitted to the central processing laboratory (JMI Laboratories, North Liberty, Iowa, USA) on provided Amies charcoal transport swabs.

Bacterial Isolates. During 2004 a total of 2,799 isolates (93.3% compliance) were processed from participant sites (range 64 to 214 isolates per site). Organism identifications were performed locally with identification confirmation achieved using colonial morphology, biochemical tests (Remel, Lenexa, Kansas, USA) and/or the Vitek System identification cards (bioMerieux, Hazelwood, Missouri, USA) at the monitoring laboratory as required.

MATERIALS AND METHODS CONTINUED

Susceptibility Testing. Susceptibility testing was performed for all Gram-negative bacterial strains utilizing Clinical Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards [NCCLS]) reference methods to determine minimum inhibitory concentrations (MICs). Inocula were prepared in sterile water equal to a 0.5 McFarland standard, diluted 1:200 in Mueller-Hinton broth, and then dispensed (100 μl; final concentration 5 x 10^5 CFU/ml) using an autoinoculator into each well of a commercially prepared, validated dry-form panel (TREK Diagnostics, Cleveland, Ohio, USA). The panels were incubated at 35°C in ambient air for 16 - 18 hours per NCCLS recommendations. NCCLS 2004 criteria were applied for interpretation of susceptibility and resistance. Quality control of the susceptibility tests methods was assured utilizing concurrent testing with American Type Culture Collection (ATCC) strains *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213.

β-Lactamase Screening. The NCCLS (2004) ESBL screening criteria (MIC, ≥ 2 μg/ml for ceftazidime or ceftriaxone or aztreonam) were applied to *E. coli*, *Klebsiella* spp. and *Proteus mirabilis* isolates. All screen-positive isolates were tested by a disk approximation method to demonstrate an enhanced ceftazidime, cefotaxime or aztreonam activity in the presence of clavulanate.

All isolates resistant to both carbapenems and ceftazidime were screened for the presence of a MBL using a disk approximation method to demonstrate EDTA or 2-mercaptopropionic acid inhibition of meropenem or imipenem hydrolysis.

RESULTS

- Table 1 summarizes the MIC_{50}, MIC_{90}, MIC range, and the percent susceptible/resistant for the seven largest genus groups or individual species that represented 97.9% of the submitted Enterobacteriaceae isolates.
- Against all enteric bacilli, meropenem and imipenem demonstrated a 99.9% susceptibility rate followed by cefepime (99.3%), amikacin (99.1%), piperacillin/tazobactam (96.0%), ceftriaxone (95.3%), aztreonam (95.1%), ceftazidime (94.7%), tobramycin (93.9%) and gentamicin (92.1%; data not shown). The fluoroquinolones, levofloxacin and ciprofloxacin, exhibited the lowest susceptibility rates at 86.9 and 86.1%, respectively (data not shown).
- Meropenem had a greater potency (four - to 32-fold higher) compared to imipenem against the seven organism groups listed in Table 1. The only carbapenem-resistant Enterobacteriaceae isolates were two strains of *K. pneumoniae* submitted from the same medical center, but possessing different antibiograms.
- The highest rates of fluoroquinolone resistance were observed among the indole-positive Proteae and *E. coli*, with 34.4 to 42.2% resistance and 20.2 to 20.7% resistance, respectively.
- ESBL phenotypes and confirmed strains were observed more frequently in *Klebsiella* spp. isolates when compared to *E. coli*. A great diversity was observed in the frequency of ESBL-producing strains between the 15 medical centers for both *E. coli* (0.0 - 12.0%; average, 4.6%) and *Klebsiella* spp. (0.0 - 23.3%; average, 6.9%).
- Against the 689 *P. aeruginosa* isolates tested, amikacin showed the highest susceptibility rate (97.0%) followed by tobramycin (91.6%) and meropenem (90.3%; Table 2).
- Meropenem (MIC_{50}, 0.5 μg/ml and MIC_{90}, 4 μg/ml) was two-fold more potent than imipenem against the *P. aeruginosa* isolates. On the other hand, imipenem was two-fold more potent than meropenem against the *Acinetobacter* spp.
- *Acinetobacter* spp. isolates showed reduced susceptibility rates to all antimicrobials tested with only amikacin (84.5% susceptible), tobramycin (84.5%), imipenem (83.8%) and meropenem (76.1%) demonstrating greater than 70% susceptibility.
- Against the collection of less frequently isolated non-enteric Gram-negative bacterial species, only the carbapenems exhibited an acceptable susceptibility rate (> 90%). This group of organisms included 12 genus groups, and was dominated by *Alcaligenes* spp. (39.2%) and *Pseudomonas* spp. (excluding *P. aeruginosa*; 27.4%).
- Figures 1 and 2 show the trends in susceptibility rates over a six-year period for selected antimicrobial agents against Enterobacteriaceae and *Acinetobacter* spp. isolates. The carbapenems have remained active at a consistent rate, but the fluoroquinolone activities have decreased significantly.

RESULTS CONTINUED

Table 1. Antimicrobial activity of meropenem tested against 1,825 Enterobacteriaceae isolated in the USA MYSTIC Programme (2004).

Organism/antimicrobial agent (no. tested)	MIC (ug/ml) 50%	90%	Range	% susceptible/resistant[a]
Citrobacter spp.[b] (141)				
Meropenem	0.03	0.03	≤0.016-4	100.0/0.0
Imipenem	0.25	1	0.06-2	100.0/0.0
Aztreonam	≤1	16	≤1->16	87.9/8.5
Ceftriaxone	≤0.25	16	≤0.25->32	88.7/5.0
Ceftazidime	0.25	>16	≤0.12->16	89.4/10.6
Cefepime	≤0.12	0.5	≤0.12-16	99.3/0.0
Piperacillin/Tazobactam	2	16	≤1->128	91.5/2.8
Amikacin	≤4	≤4	≤4-32	98.6/0.0
Gentamicin	≤1	2	≤1->8	91.5/7.8
Tobramycin	≤1	2	≤1->8	92.9/5.7
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	95.0/4.3
Levofloxacin	≤0.06	0.5	≤0.06->8	95.0/2.8
Enterobacter spp.[c] (160)				
Meropenem	0.03	0.06	≤0.016-2	100.0/0.0
Imipenem	0.25	1	0.06-2	100.0/0.0
Aztreonam	≤1	>16	≤1->16	83.8/13.8
Ceftriaxone	≤0.25	32	≤0.25->32	82.5/9.4
Ceftazidime	0.25	>16	≤0.12->16	80.6/16.3
Cefepime	≤0.12	1	≤0.12->16	98.8/0.6
Piperacillin/Tazobactam	2	32	≤1->128	86.9/5.6
Amikacin	≤4	≤4	≤4->32	97.5/1.3
Gentamicin	≤1	≤1	≤1->8	90.0/9.4
Tobramycin	≤1	8	≤1->8	88.1/8.8
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	90.0/8.8
Levofloxacin	≤0.06	0.5	≤0.06->8	90.6/7.5
Escherichia coli (724)				
Meropenem	≤0.016	0.03	≤0.016-2	100.0/0.0
Imipenem	0.12	0.12	0.03-2	100.0/0.0
Aztreonam	≤1	≤1	≤1->16	97.8/1.5 (4.4)[d]
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	97.9/1.1 (3.2)[d]
Ceftazidime	≤0.12	0.25	≤0.12->16	97.5/1.5 (3.7)[d]
Cefepime	≤0.12	≤0.12	≤0.12->16	99.3/0.4
Piperacillin/Tazobactam	2	4	≤1->128	98.5/1.1
Amikacin	≤4	≤4	≤4->32	99.9/0.1
Gentamicin	≤1	8	≤1->8	89.8/9.4
Tobramycin	≤1	4	≤1->8	94.5/2.2
Ciprofloxacin	≤0.25	>2	≤0.25->2	78.9/20.7
Levofloxacin	≤0.06	>8	≤0.06->8	79.0/20.2
Klebsiella spp.[e] (433)				
Meropenem	0.03	0.03	≤0.016->32	99.5/0.5
Imipenem	0.12	0.25	0.06->32	99.5/0.5
Aztreonam	≤1	≤1	≤1->16	94.9/4.8 (6.2)[f]
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	95.6/2.5 (6.2)[f]
Ceftazidime	≤0.12	0.5	≤0.12->16	94.7/4.6 (6.2)[f]
Cefepime	≤0.12	≤0.12	≤0.12->16	98.8/0.7
Piperacillin/Tazobactam	2	8	≤1->128	95.6/3.5
Amikacin	≤4	≤4	≤4->32	98.2/0.7
Gentamicin	≤1	≤1	≤1->8	94.9/3.9
Tobramycin	≤1	≤1	≤1->8	94.9/4.6
Ciprofloxacin	≤0.25	≤0.25	≤0.25->2	94.7/4.8
Levofloxacin	≤0.06	0.5	≤0.06->8	94.9/4.2
Proteus mirabilis (128)				
Meropenem	0.03	0.06	≤0.016-0.12	100.0/0.0
Imipenem	0.25	1	0.03-2	100.0/0.0
Aztreonam	≤1	≤1	≤1-8	100.0/0.0 (0.8)[g]
Ceftriaxone	≤0.25	≤0.25	≤0.25-4	100.0/0.0 (0.8)[g]
Ceftazidime	≤0.12	≤0.12	≤0.12-4	100.0/0.0 (2.3)[g]
Cefepime	≤0.12	≤0.12	≤0.12-4	100.0/0.0
Piperacillin/Tazobactam	≤1	≤1	≤1-2	100.0/0.0
Amikacin	≤4	≤4	≤4-32	99.2/0.0
Gentamicin	≤1	≤1	≤1->8	97.7/0.8
Tobramycin	≤1	≤1	≤1-4	100.0/0.0
Ciprofloxacin	≤0.25	2	≤0.25->2	89.8/7.0
Levofloxacin	≤0.06	2	≤0.06->8	93.8/6.3
Indole-Positive Proteae[h] (90)				
Meropenem	0.06	0.12	≤0.016-0.25	100.0/0.0
Imipenem	1	2	0.06-2	100.0/0.0
Aztreonam	≤1	8	≤1->16	95.6/3.3
Ceftriaxone	≤0.25	1	≤0.25->32	96.7/1.1
Ceftazidime	0.25	4	≤0.12->16	92.2/5.6
Cefepime	≤0.12	0.25	≤0.12-8	100.0/0.0
Piperacillin/Tazobactam	≤1	4	≤1->128	95.6/1.1
Amikacin	≤4	≤4	≤4-16	100.0/0.0
Gentamicin	≤1	≤1	≤1->8	87.8/7.8
Tobramycin	≤1	8	≤1->8	88.9/5.6
Ciprofloxacin	≤0.25	>2	≤0.25->2	56.7/42.2
Levofloxacin	0.25	>8	≤0.06->8	58.9/34.4
Serratia spp.[i] (149)				
Meropenem	0.03	0.06	≤0.016-0.25	100.0/0.0
Imipenem	0.5	1	0.12-2	100.0/0.0
Aztreonam	≤1	8	≤1->16	96.6/3.4
Ceftriaxone	≤0.25	4	≤0.25->32	95.3/1.3
Ceftazidime	0.25	0.5	≤0.12->16	96.6/2.7
Cefepime	≤0.12	0.25	≤0.12-4	100.0/0.0
Piperacillin/Tazobactam	2	8	≤1->64	95.3/0.0
Amikacin	≤4	≤4	≤4-16	100.0/0.0
Gentamicin	≤1	≤1	≤1->8	93.3/4.7
Tobramycin	2	4	≤1->8	91.3/7.4
Ciprofloxacin	≤0.25	1	≤0.25->2	94.6/1.3
Levofloxacin	0.12	1	≤0.06-4	98.0/0.0

a. Criteria as published by the NCCLS (2004).
b. Includes *Citrobacter amalonaticus* (four strains), *C. braakii* (one strain), *C. farmeri* (one strain), *C. freundii* (65 strains), *C. koseri* (37 strains) and *Citrobacter* spp. (33 strains).
c. Includes *Enterobacter aerogenes* (43 strains), *E. cloacae* (92 strains), *E. gergoviae* (one strain) and *Enterobacter* spp. (24 strains).
d. ESBL phenotype using NCCLS screening criteria of ≥ 2 μg/ml for ceftriaxone or ceftazidime or aztreonam.
e. Includes *Klebsiella ornithinolytica* (three strains), *K. oxytoca* (54 strains), *K. ozaenae* (one strain), *K. pneumoniae* (337 strains) and *Klebsiella* spp. (38 strains).
f. ESBL phenotype (confirmed strains).
g. Includes *Morganella morganii* (53 strains), *Morganella* spp. (three strains), *Proteus* spp. (five strains), *Proteus vulgaris* (one strain), *Providencia alcalifaciens* (one strain), *Providencia rettgeri* (nine strains), *Providencia* spp. (three strains) and *Providencia stuartii* (20 strains).
h. Includes *Serratia liquifaciens* (four strains), *S. marcescens* (122 strains) and *Serratia* spp. (23 strains).

Table 2. Antimicrobial activity of meropenem compared to 11 broad-spectrum antimicrobial agents tested against 933 non-fermentative Gram-negative bacilli in the MYSTIC Programme (2004).

Organism/antimicrobial agent (no. tested)	MIC (ug/ml) 50%	90%	Range	% susceptible/resistant[a]
P. aeruginosa (689)				
Meropenem	0.5	4	≤0.016->32	90.3/5.8
Imipenem	1	8	0.06->32	87.8/5.1
Aztreonam	8	>16	≤1->16	66.8/19.4
Ceftriaxone	>32	>32	≤0.25->32	11.5/78.8
Ceftazidime	2	>16	0.25->16	82.6/13.4
Cefepime	4	16	≤0.12->16	82.7/5.8
Piperacillin/Tazobactam	4	128	≤1->128	88.0/12.0
Amikacin	≤4	8	≤4->32	97.0/1.9
Gentamicin	≤1	8	≤1->8	86.8/9.9
Tobramycin	≤1	4	≤1->8	91.6/7.7
Ciprofloxacin	≤0.25	>2	≤0.25->2	73.6/21.2
Levofloxacin	0.5	>8	≤0.06->8	69.4/23.2
Acinetobacter spp.[b] (142)				
Meropenem	0.5	16	0.03->32	76.1/16.2
Imipenem	0.25	8	0.03-32	83.8/8.5
Aztreonam	>16	>16	≤1->16	12.0/72.5
Ceftriaxone	32	>32	≤0.25->32	21.1/40.8
Ceftazidime	16	>16	0.5->16	49.3/41.5
Cefepime	8	>16	0.25->16	51.4/31.7
Piperacillin/Tazobactam	16	>128	≤1->128	54.9/37.3
Amikacin	≤4	>32	≤4->32	84.5/14.1
Gentamicin	≤1	>8	≤1->8	63.4/33.8
Tobramycin	≤1	>8	≤1->8	84.5/12.7
Ciprofloxacin	0.5	>2	≤0.25->2	54.2/44.4
Levofloxacin	0.25	>8	≤0.06->8	59.9/39.4
Other non-enteric species[c] (102)				
Meropenem	0.25	4	≤0.016->32	91.2/3.9
Imipenem	0.5	4	≤0.016-32	92.2/1.0
Aztreonam	>16	>16	≤1->16	29.4/55.9
Ceftriaxone	16	>32	≤0.25->32	47.1/35.3
Ceftazidime	4	>16	≤0.12->16	82.4/12.7
Cefepime	8	>16	≤0.12->16	56.9/28.4
Piperacillin/Tazobactam	2	128	≤1->128	84.3/10.8
Amikacin	8	>32	≤4->32	63.7/34.3
Gentamicin	2	>8	≤1->8	55.9/40.2
Tobramycin	2	>8	≤1->8	54.9/43.1
Ciprofloxacin	1	>2	≤0.25->2	53.9/40.2
Levofloxacin	1	>8	≤0.06->8	66.7/23.5

a. Criteria as published by the NCCLS (2004).
b. Includes *Acinetobacter baumannii* (111 strains), *A. junii* (two strains), *A. lwoffi* (10 strains) and *Acinetobacter* spp. (19 strains).
c. Includes *Achromobacter xylosoxidans* (four strains), *Aeromonas caviae* (one strain), *A. hydrophila* (four strains), *Aeromonas* spp. (four strains), *Agrobacterium radiobacter* (two strains), *Alcaligenes faecalis* (eight strains), *Alcaligenes* spp. (10 strains), *A. xylosoxidans* (23 strains), *Burkholderia brevicapitata* (one strain), *Burkholderia cepacia* (six strains), *Chryseobacterium* spp. (one strain), *Ochrobactrum anthropi* (three strains), *Pasteurella multocida* (five strains), *Pseudomonas fluorescens* (five strains), *P. fluorescens/putida* (seven strains), *P. mendocina* (one strain), *P. oryzihabitans* (four strains), *P. putida* (six strains), *Pseudomonas* spp. (one strain), *P. stutzeri* (four strains), *Rasamsonia* spp. (two strains) and *Sphingomonas paucimobilis* (one strain).

Figure 1. Trends in susceptibility rates for selected MYSTIC Programme antimicrobial agents tested against all Enterobacteriaceae isolates tested between 1999 and 2004.

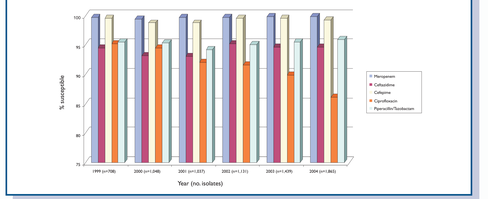
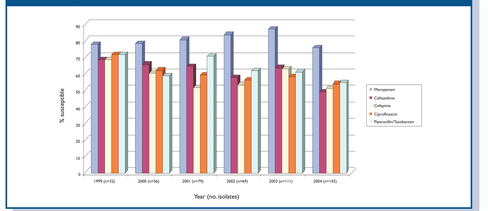


Figure 2. Trends in susceptibility rates for selected MYSTIC Programme antimicrobial agents tested against *Acinetobacter* spp. isolates tested between 1999 and 2004.



CONCLUSIONS

- In 2004, the carbapenems remained the most active broad-spectrum antimicrobial agents with meropenem MIC_{50} and MIC_{90} results at least four- to 32-fold lower than imipenem, except for *Acinetobacter* spp. isolates.
- Trend analysis based on the percent susceptibility results for the Enterobacteriaceae isolates tested within the MYSTIC Programme showed less than a ± 2% change from the 1999 baseline rate for most agents except for a steadily decreasing susceptibility rate for ciprofloxacin and other fluoroquinolones.
- Continued detection of ESBL and stably derepressed AmpC enzymes and the emergence of metallo-β-lactamases in USA MYSTIC participant sites demonstrates the need to monitor for the incidence and spread of these mechanisms of resistance within medical centers and geographic regions.
- The carbapenems remain potent antimicrobial agents necessary for the treatment of serious infections. Their efficacy can be maintained through cooperative interactions between health care providers and local, national and global surveillance efforts.
- Surveillance programs remain necessary to monitor the usefulness of antimicrobial agents against Gram-negative bacilli.

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SELECTED REFERENCES

Jones RN, Masterton R. (2001). Determining the value of antimicrobial surveillance programs. *Diagnostic Microbiology and Infectious Disease* 41:171-175.

National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial tests for bacteria that grow aerobically; Approved Standard M7-A6*. Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. (2004). *Performance standards for antimicrobial Susceptibility Testing. 14th informational supplement M100-S14*. Wayne, PA:NCCLS.

Paterson DL. (2002). Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum ß-lactamases (ESBLs). *Clinical Microbiology Infection* 6:460-463.

Pfaller MA, Jones RN, Biedenbach DJ, MYSTIC Study Group (USA). (2001). Antimicrobial resistance trends in medical centers using carbapenems: Report of 1999 and 2000 results from the MYSTIC Programme (USA). *Diagnostic Microbiology and Infectious Disease* 41:177-182.

Rasmussen BA, Bush K. (1997). Carbapenem-hydrolyzing ß-lactamases. *Antimicrobial Agents and Chemotherapy* 41:223-232.

Senda K, Arakawa Y, Ichiyama S, Nakashima K, Ito H, Ohsuka S, Shimokata K, Kato N, Ohta M. (1996). PCR detection of metallo-ß-lactamase gene ($blaIMP$) in Gram-negative rods resistant to broad-spectrum ß-lactams. *Journal of Clinical Microbiology* 34:2909-2913.

Toleman MA, Rolston K, Jones RN, Walsh TR. (2004). $blaVIM-1$, an evolutionarily distinct metallo-ß-lactamase gene in a *Pseudmonas aeruginosa* isolate from the United States. *Antimicrobial Agents and Chemotherapy* 48:329-332.

Turner PJ. (2000). MYSTIC (Meropenem Yearly Susceptibility Test Information Collection), a global overview. *Journal of Antimicrobial Chemotherapy* 46:9-23.

Turner PJ. (2004). Susceptibility of meropenem and comparators tested against 30,634 Enterobacteriaceae isolated in the MYSTIC Programme (1997 - 2003). *Diagnostic Microbiology and Infectious Disease* 50:291-293.