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In vitro activity of meropenem, imipenem, piperacillin/tazobactam, ciprofloxacin, amikacin, and cefepime against *P. aeruginosa* and *A. baumannii* isolated from Brazilian intensive care units - MYSTIC Study Group (Brazil 2001)

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On behalf of the MYSTIC Study Group

The selection of multiresistant bacteria has increased subsequent to the introduction of a large number of antibiotics with various mechanisms of action. The scale of this problem is best exemplified by the fact that most nosocomial infection, mainly in ICUs, involve multiresistant bacteria producing several types of enzymes such as extended spectrum β-lactamases, depression of chromosomal *ampC* β-lactamases, plasmid-coded *ampC* β-lactamases in members of Enterobacteriaceae, and multiresistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. In this study, the in vitro activities of meropenem (MEM), imipenem (IMP), piperacillin/tazobactam (PIP/TAZ), ciprofloxacin (CIP), amikacin (AMI), and cefepime (CPM) were monitored and compared against 135 ICU isolates of *Pseudomonas aeruginosa* (*n* = 90) and *Acinetobacter baumannii* (*n* = 45). Minimal Inhibitory Concentrations (MICs) were determined by E-test methodology, using standardized and controlled procedures. Overall susceptibility results, MIC_{50} and MIC_{90} values are shown in the table below. A high rate of resistance was noticed among the tested strains. Meropenem was the most active agent against both species evaluated. Additionally, the MICs for *P. aeruginosa* were steadily lower when compared to imipenem. Towards *Acinetobacter baumannii*, performances of meropenem and imipenem were similar, showing much superior efficacy comparing to other class of agents.
Currently, as we can see, there are few alternative therapies for infections caused by these two species. Infection control measures, rational antibiotic policies and rapid laboratory detection of resistance are the key measures in preventing the spread of these strains.

	P. aeruginosa (*n* = 90)					*A. baumannii* (*n* = 45)				
	%S	%I	%R	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	%S	%I	%R	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
MEM	72.2	7.8	20	0.38	>32.0	93.3		6.7	1.0	2.0
IMP	66.7	3.3	30	1.0	>32.0	93.3		6.7	0.5	2.0
PIP/TAZ	76.7		23.3	4.0	>256.0	24.4	8.9	66.7	>256.0	>256.0
CIP	53.3	2.2	44.5	0.38	>32.0	22.2	2.2	75.6	>32.0	>32.0
AMI	60	4.4	35.6	8.0	>256.0	22.2	11.1	66.7	>256.0	>256.0
CPM	71.1	11.1	17.8	4.0	32.0	26.7	2.2	71.1	96.0	>256.0

IN-VITRO ACTIVITY OF MEROPENEM AND COMPARATORS AGAINST *P. AERUGINOSA* AND *A. BAUMANNII* ISOLATED FROM BRAZILIAN INTENSIVE CARE UNITS - RESULTS OF MYSTIC BRAZIL 2001

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MYSTIC
Meropenem Yearly Susceptibility Test Information Collection

SUMMARY

The selection of multi-resistant bacteria has increased subsequently with the introduction of a large number of antibiotics with various mechanisms of action. The scale of this problem is best exemplified by the fact that most nosocomial infections involve multi-resistant bacteria. These produce several types of enzymes such as extended spectrum β-lactamases, derepression of chromosomal AmpC β-lactamases, plasmid-coded AmpC β-lactamases in members of Enterobacteriaceae, and multi-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.
In this study, the in-vitro activities of meropenem (MEM), imipenem (IPM), piperacillin/tazobactam (TAZ), ciprofloxacin (CIP), amikacin (AMK), and cefepime (CPE) were monitored and compared against 135 intensive care unit (ICU) isolates of *P. aeruginosa* (n=90) and *A. baumannii* (n=45). Minimum inhibitory concentrations (MICs) were determined by E-test methodology, using standardised and controlled procedures. Against *P. aeruginosa*, TAZ showed the highest rate of susceptibility (76.7%) followed by MEM (72.2%), CPE (71.1%), IPM (66.7%), AMK (60%), and CIP (53.3%). Towards *A. baumannii*, performances of MEM and IPM were similar (93.3% susceptible), showing much superior efficacy compared with other classes of agent. As already expected, a high rate of resistance was noticed among the tested strains. MEM was relatively active against both species evaluated. Additionally, the MICs for *P. aeruginosa* were consistently lower when compared with IPM. Based on current resistance trends among Gram-negative nosocomial pathogens, carbapenems may now be one of the best therapeutic alternatives to be used with confidence as empiric monotherapy in intensive care units.

INTRODUCTION

Much has been written in recent years about the ever-increasing problem of the numbers of clinically important bacteria that have developed resistance to a wide range of antibacterial agents. The establishment of several surveillance programmes has provided important information about changes in the spectrum of microbial pathogens and antimicrobial resistance patterns in nosocomial and community-acquired infections. This information has proved useful in the development of empirical approaches for the treatment of serious infections, and may be of use in the prevention and control of infections caused by multi-resistant organisms. Furthermore, surveillance has provided evidence of important differences in antimicrobial resistance patterns that may occur in various geographical regions. Additionally, surveillance efforts stimulate epidemiological research, leading to improved control and prevention strategies.

Gram-negative organisms are extremely important nosocomial pathogens, eg they are a major cause of septic shock with a very high rate of associated mortality. ICUs are probably the greatest risk areas of a hospital with regard to rate of nosocomial infections and incidence of multi-drug resistance among clinical isolates. The emergence of resistance to antimicrobials among Gram-negative isolates, eg members of Enterobacteriaceae and non-fermenters (*P. aeruginosa* and *A. baumannii*), has become a serious problem in recent years. Resistance is generally more common in the presence of greater antibiotic usage, notably in the ICU setting.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Programme was established to monitor the performance of MEM and comparator broad-spectrum agents against significant pathogens isolated from infected patients hospitalised in units where MEM is prescribed.

The present report summarises the in-vitro activity of MEM and five comparator drugs tested against *P. aeruginosa* and *A. baumannii* isolated from Brazilian ICUs.

METHODS

Strains

- One hundred and thirty-five Gram-negative bacilli (90 *P. aeruginosa* and 45 *A. baumannii*) were selected randomly for inclusion in this study.
- All isolates were collected consecutively from patients hospitalised in ICUs of several Brazilian hospitals during 2000-2001. Multiple isolates of the same species with single origin (same patients) were excluded.
- Identification of species was performed by each participant laboratory and confirmed by the coordinator laboratory (Fleury - Medical Diagnostic Center) either using conventional biochemical methodology or automated system (Vitek).

Antimicrobial agents and susceptibility testings

- Isolates were submitted to susceptibility testing for MEM, IPM, TAZ, CIP, AMK, and CPE.
- MICs were determined using the Etest methodology (AB Biodisk - Probac Brazil) on Mueller Hinton agar, and interpreted according to the criteria of the National Committee for Clinical Laboratory Standards.[1]
- Control strains of *Escherichia coli* (ATCC 25922), and *P. aeruginosa* (ATCC 27853) were run with each set of MIC determinations.

RESULTS

P. aeruginosa

- High rates of resistance were observed (Table 1). TAZ presented the best performance against *P. aeruginosa* followed by MEM, CPE, IPM, AMK and CIP (Table 1).
- MEM and CIP presented the lowest MIC_{50} (Table 1, Figure 1).
- There were alarming non-susceptibility rates towards CIP (46.7%) and AMK (40%).
- Four isolates presented significantly lower MICs to MEM than IPM.
- A small increase in resistance of *P. aeruginosa* to the carbapenems was observed when year 2001 data was compared with 2000 data (Figure 2). MICs will continue to be monitored to determine whether this is a trend or not.

Table 1. Overall susceptibility results

	Pseudomonas aeruginosa (n=90)					*Acinetobacter baumannii* (n=45)				
	% S	% I	% R	MIC_{50}	MIC_{90}	% S	% I	% R	MIC_{50}	MIC_{90}
MEM	72.2	7.8	20.0	0.38	>32	93.3	-	6.7	1	2
IPM	66.7	3.3	30.0	1	>32	93.3	-	6.7	0.5	2
TAZ	76.7	-	23.3	4	>256	24.4	8.9	66.7	>256	>256
CIP	53.3	2.2	44.5	0.38	>32	22.2	2.2	75.6	>32	>32
AMK	60.0	4.4	35.6	8	>256	22.2	11.1	66.7	>256	>256
CPE	71.1	11.1	17.8	4	32	26.7	2.2	71.1	96	>256

Figure 1. Cumulative % inhibition of *P. aeruginosa* (n=90)

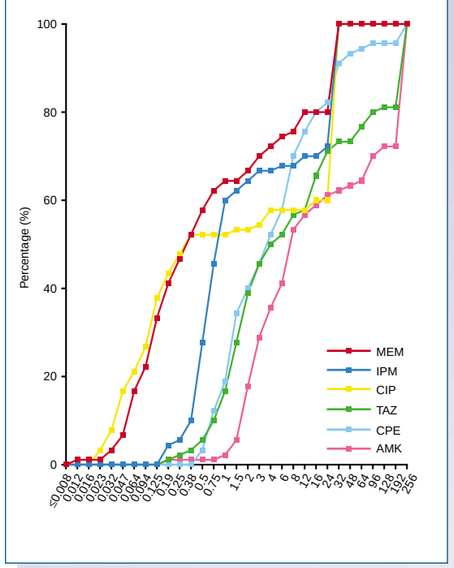
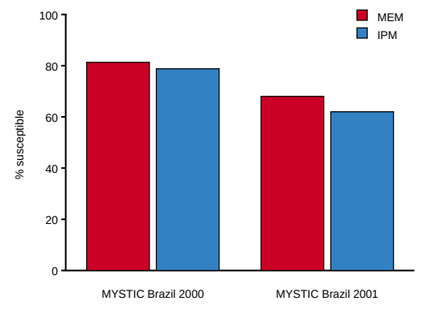


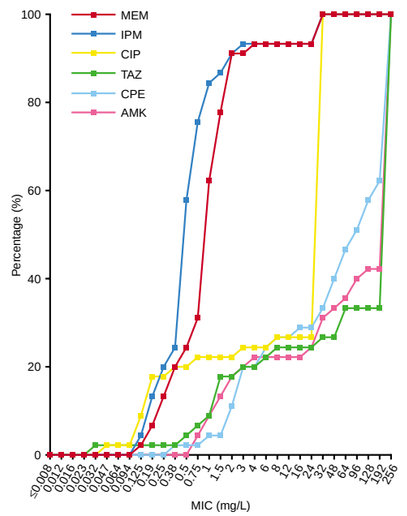
Figure 2. Susceptibility differences in *P. aeruginosa* for 2001 versus 2000



A. baumannii

- % susceptibilities/resistances to MEM and IPM were equivalent (Table 1).
- IPM presented a slightly lower MIC_{50} than MEM (Table 1, Figure 3).
- Carbapenems had much higher in-vitro activity than other classes of antimicrobials. Susceptibilites of TAZ, CIP, AMK, and CPE were in the mid-20% range (Table 1).

Figure 3. Cumulative % inhibition of *A. baumannii* (n=90)



CONCLUSIONS

- **MEM, TAZ and CPE were relatively more active against isolates of *P. aeruginosa* than other antimicrobial agents.**
- **MEM and IPM were by far the most active antimicrobial agents against isolates of *A. baumannii*.**
- **Based on these findings, and those of previous MYSTIC Programme results and other surveillance studies, carbapenems may be the main therapeutic choice in the empiric monotherapy of serious infections caused by *P. aeruginosa* and *A. baumannii* in ICU patients in Brazil.**

REFERENCE

1. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Fifth Edition: Approved Standard Document M7-A5. NCCLS, Wayne, PA, 2000.