Antimicrobial Susceptibility in Intensive Care Units: MYSTIC Program Brazil 2002

Caio Mendes[1], Carmen Oplustil[1], Elsa Sakagami[1], Philip Turner[2], Carlos Kiffer[1], and the MYSTIC Brazil Group

Fleury Institute, Advisory Group on Antimicrobials and Clinical Microbiology[1], São Paulo, SP, Brazil; AstraZeneca Pharmaceuticals[2], Macclesfield, Cheshire, England

Objective. Establish the susceptibility pattern of Gram-negative bacteria causing infections in ICU patients, MYSTIC Program Brazil 2002. **Material and Methods.** Gram-negative bacteria (n = 503) causing nosocomial infections were collected at seven Brazilian centers. The central laboratory confirmed the identification and performed the susceptibility tests by E-test methodology (AB Biodisk, Solna, Sweden) for meropenem, imipenem, ciprofloxacin, ceftazidime, cefepime, cefotaxime, piperacillin/tazobactam, gentamicin, and tobramycin. Interpretation criteria used were according to National Committee for Clinical Laboratory Standards (NCCLS). **Results.** *Pseudomonas aeruginosa* (33%) was the most frequently isolated, followed by *A. baumannii* (17.1%), *K. pneumoniae* (12.1%), *E. coli* (10.5%), and *E. cloacae* (7.9%). *Pseudomonas aeruginosa* isolates had susceptibility rates of 67.5% to piperacillin/tazobactam, 59.8% to meropenem, 57.3% to imipenem. *A. baumannii* presented susceptibility rates to meropenem of 89.5%, 88.4% to imipenem, and 74.4% to tobramycin. *E. coli* and *K. pneumoniae* were fully susceptible to both carbapenems. **Conclusions.** Carbapenem resistance among Enterobacteriaceae is still rare in this region. *A. baumannii* and *P. aeruginosa* presented elevated resistance rates to all antimicrobials. Since these two bacterial species play an important role in nosocomial infections, the use of empirical combination therapy to treat these pathogens may be justified.
Key Words: Drug resistance, bacterial, microbial sensitivity tests, infection control, carbapenems.

Antimicrobial resistance among pathogens causing hospital-acquired infections is a major worldwide issue, which must be dealt with continuously [1-4]. Surveillance programs are valuable tools and offer important information on bacterial resistance trends, by geographical location and by disease type in community and hospital settings. Several studies have reported higher rates of antimicrobial resistance among isolates from intensive care units (ICUs) than among

isolates from general patient-care areas [1,5-7]. Consequently, proper surveillance programs focused on specific patient-care areas have become a focal point in combating the development of resistant organisms [3-5,7-13]. Furthermore, information on the minimum inhibitory concentration (MIC) generated by such programs help guide antimicrobial therapy before susceptibility tests are available, and they may help prevent the overuse of certain compounds [9]. However, surveillance programs are limited in their ability to address all relevant clinical and microbiological outcome issues. Thus, efforts must be made to better understand bacterial resistance trends and to refine clinical decision tools locally. The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) program is a global, annual and multicenter surveillance study that compares the activity of several broad-spectrum antimicrobial agents in carbapenem user

centers. These data could be used, in conjunction with other related studies, to properly interpret significant resistance patterns and choose the most appropriate antimicrobial regimens for empirical therapy.

The objective of our study was to determine the susceptibility pattern of Gram-negative bacteria causing nosocomial infections in ICU patients, as part of the third edition of MYSTIC Program Brazil during 2002.

Material and Methods

Full details of the study design and susceptibility testing methods have been previously described [14,15].

Participating centers

All isolates were collected during 2002 from hospitalized patients form seven ICUs in four Brazilian cities. Centers 1, 4, 6, 7 were located in São Paulo, center 2 in Florianópolis, center 3 in Rio de Janeiro, and center 5 in Brasília (Table 1).

Table 1. Number of isolates (n) and contribution (%) per center – MYSTIC Program Brazil 2002

Center	N	%
1	100	19.9
2	70	13.9
3	69	13.7
4	76	15.1
5	24	4.8
6	52	10.3
7	112	22.3
Total	**503**	**100**

Isolates

Five hundred and three Gram-negative bacilli responsible for the infections, based on the judgment of the investigators, were randomly selected at each center for this study. Multiple isolates of the same species from a single origin (same patient) were excluded. Non-sterile samples were submitted to semi-quantitative/quantitative cultures (catheter, bronchoalveolar lavage). Each participating laboratory identified the microorganisms. The central laboratory (Fleury–Medical Diagnostic Center) confirmed the identification through conventional biochemical methodology or with the Vitek automated system.

Susceptibility tests

The central laboratory determined the minimum inhibitory concentrations (MICs) of meropenem, imipenem, ciprofloxacin, ceftazidime, cefepime, cefotaxime, piperacillin/tazobactam, gentamicin, and tobramycin by E-test methodology (AB Biodisk, Solna, Sweden), and interpretations were made according to National Committee for Clinical Laboratory Standards [16]. Control strains, *E. coli* (ATCC 25922), *E. coli* (ATCC 35218), and *Pseudomonas aeruginosa* (ATCC 27853), were tested with each set of MIC determinations.

Screening for extended spectrum β-lactamase (ESBL)

Escherichia coli and *K. pneumoniae* with MICs ≥ 2 μg/mL to any cephalosporins were submitted to the ESBL production test by double-disk synergy with amoxicillin/clavulanic acid and ceftazidime, ceftriaxone, cefotaxime, and aztreonam. Isolates with enhanced zones for any of the above-mentioned agents or for amoxicillin/clavulanic acid were considered ESBL producers for the purpose of this report; this test is not recommended by the NCCLS for confirmation of ESBL production. Control strains *K. pneumoniae* (ATCC 700603 – ESBL positive) and *E. coli* (ATCC 25922 – ESBL negative) were assayed with each test set.

Results

Isolates

The prevalence of the isolated microorganisms is shown in Table 2. *Pseudomonas aeruginosa* (33%)

was the most frequent isolate, followed by *A. baumannii* (17.1%), *K. pneumoniae* (12.1%), *E. coli* (10.5%), and *E. cloacae* (7.9%).

Table 2. Prevalence of isolated microorganisms

Microorganism	n	%
P. aeruginosa	166	33.0
A. baumannii	86	17.1
K. pneumoniae	61	12.1
E. coli	53	10.5
E. cloacae	40	7.9
S. marcescens	28	5.6
P. mirabilis	16	3.2
S. maltophilia	11	2.2
A. calcoaceticus	7	1.4
B. cepacia	7	1.4
Others	27	5.6
Total	**503**	**100**

Sample sources

Table 3 shows the sample source distribution, with the most frequent samples being from blood/catheters (39.2%), followed by respiratory (25.7%) and urinary tracts (16.7%). Table 4 shows the frequency of microorganisms per sample source.

Table 3. Sample source distribution (%)

Sample	N	%
Blood/catheter	197	39.2
Respiratory tract	129	25.7
Urinary tract	84	16.7
Skin/soft tissue	33	6.5
Others	60	11.9
Total	**503**	**100**

Susceptibility patterns

Table 5 shows the overall results of susceptibility pattern of *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, and *E. coli*.

Pseudomonas aeruginosa

Pseudomonas aeruginosa (n=166) isolates presented susceptibility rates of 67.5% to piperacillin/tazobactam (MIC_{50} 24 µg/mL), 59.8% to meropenem (MIC_{50} 0.75 µg/mL), 57.3% to imipenem (MIC_{50} 2 µg/mL), 55.4% to cefepime (MIC_{50} 4 µg/mL), and 53.6% to ciprofloxacin (MIC_{50} 16 µg/mL). Ceftazidime, gentamicin and tobramycin presented susceptibility rates of < 50%.

Susceptibility of *P. aeruginosa* by center is described in Table 6, with susceptibility rates shown for all six ICUs. Center 5 is not shown due to the small number of isolates of *P. aeruginosa* (n = 5).

A. baumannii

A. baumannii (n=86) isolates presented susceptibility rates to meropenem of 89.5% (MIC_{50} 1 µg/mL), 88.4% to imipenem (MIC_{50} 0.75 µg/mL), and 74.4% to tobramycin (MIC_{50} 1.5 µg/mL). All remaining antimicrobials gave considerably lower susceptibility rates (< 55%).

K. pneumoniae

Among *K. pneumoniae* (n=61) isolates, all were susceptible to imipenem and meropenem (MIC_{90} 0.25 and 0.094 µg/mL, respectively), with susceptibility rates of 86.9% to piperacillin/tazobactam and 72.1% to ciprofloxacin. Susceptibility to cephalosporins was 62.3%, due to ESBL production in 23/61 (37.7%).

E. coli

Among *E. coli* (n = 53) isolates, all were susceptible to imipenem and meropenem (MIC_{90} 0.25 and 0.032 µg/mL, respectively), with susceptibility rates of 98.1% to piperacillin/tazobactam and 75.5% to ciprofloxacin. Susceptibility to cephalosporins was 86.8%, due to ESBL production in 7/53 (13.2%).

Discussion

The MYSTIC Program has generated a large data set for nosocomial isolates, with information on their

Table 4. Frequency of microorganisms per sample source

Microorganism	N (%)			
	Blood/Catheter	Respiratory tract	Urinary tract	Soft tissue
P. aeruginosa	44 (22.3)	52 (40.3)	31 (36.9)	19 (57.6)
A. baumannii	41 (20.8)	22 (17.1)	16 (19.0)	3 (9.1)
K. pneumoniae	27 (13.7)	12 (9.3)	10 (11.9)	3 (9.1)
E. coli	19 (9.6)	5 (3.9)	14 (16.7)	3 (9.1)
E. cloacae	22 (11.2)	10 (7.8)	2 (2.4)	3 (9.1)
S. marcescens	14 (7.1)	9 (7.0)	1 (1.2)	1 (3.0)
Others	30 (15.2)	19 (14.6)	10 (11.9)	1 (3.0)
Total n (%)	**197 (39.2)**	**129 (25.7)**	**84 (16.7)**	**33 (6.5)**

MICs. The data aggregated in our study was collected consecutively from patients hospitalized in ICUs in seven centers in Brazil during the 2002 edition of the MYSTIC Program. The program's main objective was to evaluate the susceptibility pattern of Gram-negative bacilli isolated from nosocomial infections. This is in accordance with the fundamentals of other microbiological surveillance studies, since these studies aim to identify regional patterns of resistance in specific settings. Surveillance programs also play a role as major contributors for guiding empirical antimicrobial therapy [8,9]. However, these programs are limited in their ability to answer all relevant clinical and microbiological outcome issues for all world regions, thus reinforcing the need for regional data.

Pseudomonas aeruginosa was identified in 33% of the isolates, followed by *A. baumannii* (17.1%), *K. pneumoniae* (12.1%), *E. coli* (10.5%) and *E. cloacae* (7.9%). The frequencies of *P. aeruginosa* and *A. baumannii* have risen significantly, when compared to the first MYSTIC edition in Brazil [19], but they have remained constant since the previous edition in 2001 [20]. This is probably due to the inclusion of new centers in the 2001 and 2002 editions and to the exclusive isolation of Gram-negative bacteria during both years. It should also be noted that, on the one hand, at least 55.9% of samples in the current edition were from clinically significant sources, either due to presumed sterility or to quantitative methods (blood, catheter and urinary tract). On the other hand, 25.7%

of the samples were from the respiratory tract, although always considered by investigators as causative agents of the infectious processes. Nevertheless, one cannot rule out completely the contribution of colonizers as part of the group of isolates. However, we believe that our study closely reflects the prevalence of Gram-negative bacteria causing nosocomial infections in the units that we evaluated. The high number of isolates from blood/catheters was expected, since we did not aim at establishing the prevalence of nosocomial infections. We concentrated on isolating clinically significant bacteria causing the infectious processes.

The susceptibility patterns detected by the MYSTIC Program in these seven Brazilian centers demonstrated resistance rates somewhat higher than the ones determined by other studies [4,6,7,12,17,18]. Previous editions of the MYSTIC Program in Brazil reported *P. aeruginosa* and *A. baumannii* sensitivities to carbapenems of 79%-82% and 85%-86%, respectively [19,20]. Possible reasons for the higher resistance patterns observed in our study edition could be based on the program's selection of carbapenem user hospital units and of specialized centers, particularly intensive care units (ICUs). Other possible reasons could also be that all the centers but one were located in the south and southeast region of the country, which may reflect a specific influence of demographic characteristics of ICUs in the high resistance rates obtained. Furthermore, clonal spread among *P. aeruginosa* and *A. baumannii* within specific regions

Table 5. Susceptibility patterns of *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* – MYSTIC Program Brazil 2002

Species/antimicrobial	%			μg/mL	
	S	I	R	MIC_{50}	MIC_{90}
***P. aeruginosa* (n = 166)**					
Cefepime	55.4	20.5	24.1	4	>256
Ceftazidime	31.4	12.8	55.8	>192	>256
Imipenem	57.3	6.6	36.1	2	>32
Meropenem	59.8	7.1	33.1	0.75	>32
Piperacillin/tazobactam	67.5	2.4	30.1	24	>256
Ciprofloxacin	53.6	10.2	36.2	16	>32
Gentamicin	47.6	0.0	52.4	16	>256
Tobramycin	44	0.6	55.4	12	>256
***A. baumannii* (n = 86)**					
Cefepime	31.4	37.2	31.4	64	>256
Ceftazidime	31.4	12.8	55.8	>128	>256
Imipenem	88.4	1.2	10.4	0.75	>32
Meropenem	89.5	0.0	10.5	1	>32
Piperacillin/tazobactam	40.7	12.8	46.5	64	>256
Ciprofloxacin	31.4	12.8	55.8	32	>32
Gentamicin	53.5	10.5	36	4	>256
Tobramycin	74.4	7	18.6	1.5	>256
***K. pneumoniae* (n = 61)**					
Cefepime	62.3	0.0	37.7	0.094	>32
Ceftazidime	62.3	0.0	37.7	0.25	>32
Cefotaxime	62.3	0.0	37.7	0.125	>256
Imipenem	100	0.0	0.0	0.19	0.25
Meropenem	100	0.0	0.0	0.032	0.094
Piperacillin/tazobactam	86.9	4.9	8.2	2	>256
Ciprofloxacin	72.1	6.5	21.4	0.023	>32
Gentamicin	65.6	3.4	31	0.75	>256
Tobramycin	60.7	—-	39.3	0.75	>256
***E. coli* (n = 53)**					
Cefepime	86.8	0.0	13.2	0.032	>32
Ceftazidime	86.8	0.0	13.2	0.125	>32
Cefotaxime	86.8	0.0	13.2	0.047	>256
Imipenem	100	0.0	0.0	0.19	0.25
Meropenem	100	0.0	0.0	0.016	0.032
Piperacillin/tazobactam	98.1	0.0	1.9	1	2
Ciprofloxacin	75.5	0.0	24.5	0.008	>32
Gentamicin	84.9	0.0	15.1	0.5	48
Tobramycin	86.7	0.0	13.2	0.5	32

Table 6. Susceptibility of *P. aeruginosa* (%S) per center – MYSTIC Program Brazil 2002

	% Susceptible
	C	**CFT**	**I**	**M**	**P/T**	**CPR**	**G**	**T**
Center 1	24.3	16.2	24.3	27	29.7	21.6	24.3	16.2
Center 2	95.2	85.7	100	100	100	85.7	81	81
Center 3	62.5	75	87.5	87.5	87.5	31.2	50	43.8
Center 4	50	50	45	45	55	35	45	35
Center 5*	—-	—-	—-	—-	—-	—-	—-	—-
Center 6	40.9	40.9	36.4	36.4	59.1	31.8	27.3	27.3
Center 7	75.6	75.6	75.6	82.2	88.9	62.2	66.7	66.7
Total	**55.4**	**31.4**	**57.3**	**59.8**	**67.5**	**53.6**	**47.6**	**44**

C =cefepime;CFT =ceftazidime; I=imipenem; M=meropenem;P/T=piperacillin/tazobactam;
CPR=ciprofloxacin; G=gentamicin; T=tobramycin. * Center 5 – not listed, only 5 isolates.

was detected and is currently under more extensive evaluation by investigators (CK, CM).

Pseudomonas aeruginosa (n=166) isolates had quite high resistance rates against all antimicrobials, with descending order of susceptibility rates of 67.5% to piperacillin/tazobactam (MIC_{50} 24 µg/mL), 59.8% to meropenem (MIC_{50} 0.75 µg/mL), and 57.3% to imipenem (MIC_{50} 2 µg/mL). Susceptibility of *P. aeruginosa* varied greatly among the centers, with rates ranging from 100% susceptible for carbapenems and piperacillin/tazobactam in center 2 to < 30% susceptible for all antimicrobials in center 1. As previously mentioned, clonal spread may have contributed to the susceptibility observed in specific centers. On the other hand, *A. baumannii* (n=86) isolates presented susceptibility rates to meropenem of 89.5% (MIC_{50} 1µg/mL), 88.4% to imipenem (MIC_{50} 0.75 µg/mL), and 74.4% to tobramycin (MIC_{50} 1.5 µg/mL), which is in accordance with previous MYSTIC editions in our country [19,20]. *Escherichia coli* ESBL-producing isolates (13.2%) presented prevalences similar to those of previous editions of this study [19,20]. However, *K. pneumoniae* ESBL-producing isolates presented lower prevalence rates (37.7%), when compared to the previous edition (63.5% in the 2001 edition) [20]. Tendency analysis will be performed with future editions of the program, in order to check this finding.

Additionally, results from the 2002 edition of the MYSTIC Program in Brazil, Colombia, Peru and Venezuela were also used in the international program for pharmacodynamic comparisons, based on Monte Carlo simulation methods [21]. This program, named OPTAMA, identified differences in pharmacodynamic target attainment for commonly-used antimicrobials in South America. It also showed some discordance with percent susceptibility for certain agents, meaning that the use of pharmacodynamic target attainment may be a more accurate predictor of microbiological success. Thus, we concluded that: a) any of the carbapenems or cephalosporins would be appropriate empirical therapy when *E. coli* is suspected; b) the carbapenems should be the agents of choice for suspected *K. pneumoniae* infections; c) since no single regimen had high target attainment against *A. baumannii* and *P. aeruginosa*, the use of combination therapy to treat these pathogens in South America may be justified.

In conclusion, resistance development to antimicrobials is currently a major concern for the medical community worldwide, since infections caused by resistant bacteria seems to be associated with worsened morbidity factors (hospitalization, death and illness rates) [22]. The implementation of monitoring programs is an important part of the preventative strategy against progression of resistance. Surveillance in ICUs apparently offers a unique opportunity to detect

the emergence of resistance in bacteria used as sentinel agents, especially in units with high antibiotic usage densities [1,23]. Our study confirms previous findings that carbapenem resistance among Enterobacteriacea is still rare in this region [4,6,7,12,17-20]. On the other hand, *A. baumannii* and *P. aeruginosa* have become particularly problematic organisms in Brazil, because of their prevalence and resistance patterns. Since *A. baumannii* and *P. aeruginosa* play an important role in nosocomial infections in this environment, added to the fact that they were not highly susceptible to any of the drugs, and because no single regimen had high target attainment in data generated with a Monte Carlo simulation program using the same data [21], the use of empirical combination therapy to treat these pathogens may be justified.

MYSTIC Study Group Brazil

Jorge Sampaio, André Hsiung, Marcelo Marotti, Jorge B. Amarante, Hélio Sader, Suzane Silbert, Cássia M. Zocolli, Jorge D. de Mattos, Beatriz M. Moreira, Marinês D. Martino, Luis F. Camargo, Adília Segura, Julival Ribeiro, Lycia Mimica, Sueli Ykko.

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