Antimicrobial Susceptibility of Gram-Negative Bacteria in Brazilian Hospitals: The MYSTIC Program Brazil 2003

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Establish the susceptibility pattern of Gram-negative bacteria causing infections in ICU patients, MYSTIC Program Brazil 2003. Gram-negative bacteria (n = 1,550) causing nosocomial infections were collected at 20 Brazilian centers. The central laboratory confirmed the identification and performed the susceptibility tests by Etest 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). *Pseudomonas aeruginosa* (30.3%) was the most frequent isolate, followed by *E. coli* (18.6%), *Klebsiella pneumoniae* (16.9%), *Acitenobacter baumannii* (8.8%), and *Enterobacter cloacae* (7.1%). *Pseudomonas aeruginosa* (n=470) isolates presented susceptibility rates of 64% to meropenem, 63.8% to piperacillin/tazobactam, 63.4% to amikacin, 58.7% to imipenem. *Acitenobacter baumannii* presented susceptibility rates to meropenem of 97.1%, and 73% to tobramycin. *E. coli* and *K. pneumoniae* were highly susceptible to both carbapenems.Carbapenem resistance among the Enterobacteriaceae is still rare in the region. *Acitenobacter baumannii* and *P. aeruginosa* presented elevated resistance rates to all antimicrobials. Since they play an important role in nosocomial infections in this environment, the use of empirical combination therapy to treat these pathogens may be justified.

Key Words: Drug resistance, bacterial, microbial sensitivity tests, infection control, carbapenems.

A major issue confronting organized health care today is that of controlling the increase in antimicrobial resistance [1-4]. Although multiple factors play a role in this problem, the selective pressures induced by inappropriate and widespread use of antibiotics are considered important contributors. 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]. These studies have provided important information about changes in the spectrum of microbial pathogens and trends in antimicrobial resistance patterns in nosocomial and community-acquired infections along time. The information generated by surveillance programs, associated with an increased awareness about evolving resistance patterns, have proved helpful for the development of empirical approaches for the treatment of serious infections [8]. Additionally, surveillance programs may also be useful in the prevention and control of infections caused by resistant organisms [3-5,7-13]. Furthermore, surveillance programs have provided evidence of important differences in antimicrobial resistance patterns occurring in various geographical areas and even units within a certain area. However, those programs have a limited ability to identify and analyze all the relevant risk factors associated with the different resistance patterns.

The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) is a global, annual

Received on 10 January 2005; revised 07 June 2005.

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The Brazilian Journal of Infectious Diseases 2005;9(3):216-224

and multicenter surveillance program that compares the activity of several broad-spectrum antimicrobial agents in carbapenem user centers. MYSTIC Program Brazil was started in 1999, involving three centers (ICUs only); it was increased to seven centers in 2001 and 2002 (ICUs only), and matured to the present 2003 edition, with 20 centers (12 ICUS, 2 neutropenic patient units, and 6 general wards).

The objective of our study was to determine the susceptibility pattern of Gram-negative bacteria causing nosocomial infections in hospital patients, as part of the fourth edition of MYSTIC Program Brazil during 2003. It is our intention that these data could then be used locally, in conjunction with other related studies, to properly interpret significant resistance patterns and choose the most appropriate antimicrobial regimens for empirical therapy.

Material and Methods

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

Participating Centers

There were 19 participating centers during the 2003 program edition. All centers were asked to submit up to 100 Gram-negative bacteria samples, representative of the infectious process, regardless of the sample source, from specialized hospital units. All isolates were collected from January to October 2003 from hospitalized patients in 12 ICUs, 2 neutropenic patient units, and 6 general wards. Among the participating centers, 10 were located in southeastern (7 in São Paulo, 2 in Rio de Janeiro, 1 in Minas Gerais), 7 in southern (4 in Rio Grande do Sul, 2 in Paraná, 1 in Santa Catarina), 2 in northeastern (Bahia), and 1 in midwest Brazilian states (Brasilia) (Table 1).

Isolates

One thousand five hundred and fifty Gram-negative bacilli responsible for the infectious process (according to the investigators) were randomly selected for inclusion in this study. Multiple isolates of the same species from a single origin (same patient) were excluded. Catheter, tracheal aspirates and bronchoalveolar lavage samples were submitted to semi-quantitative/quantitative cultures, accordingly. Each participating laboratory performed identification of microorganisms. The central laboratory (Fleury Diagnostics) confirmed the identification through conventional biochemical methodology or through 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, tobramycin, and amikacin by Etest methodology (AB Biodisk, Solna, Sweden) and interpretations were made according to National Committee for Clinical Laboratory Standards (NCCLS) [16]. Control strains of *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)

E. coli and *K. pneumoniae* with MICs ≥ 2 μg/mL to any cephalosporins were submitted to an ESBL production test by double-disk synergy with amoxicillin/clavulanic acid and ceftazidime, ceftriaxone, cefotaxime, and aztreonam. Isolates with an enhanced zone for any of these agents and amoxicillin/clavulanic acid were considered ESBL producers for the purpose of this report [17], since 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.

For the remaining species of *Enterobacteriaceae*, isolates that produced intermediate to resistant MICs to cefepime were interpreted as compatible with a

phenotype of ESBL and AmpC producers. Strains with reduced susceptibility (I or R) to cefotaxime and ceftazime but susceptible to cefepime, were submitted to the double-disk synergy test to distinguish between AmpC hyperproduction and ESBL production phenotypes.

Results

Isolates

The prevalence of microorganisms isolated and submitted to the central lab is shown in Table 2. *Pseudomonas aeruginosa* (30.3%) was the most frequently-sent isolate, followed by *E. coli* (18.6%), *K. pneumoniae* (16.9%), *A. baumannii* (8.8%), and *Enterobacter cloacae* (7.1%).

Sample Sources

Regarding sample source distribution, the most frequent samples were from urinary tract (31.2%), followed by blood/catheter (26.3%), respiratory tract (17.1%) and intra-abdominal samples (2.9%) (Table 3).

Susceptibility Patterns

Table 4 shows the overall results of susceptibility pattern of *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and *A. baumannii*.

P. aeruginosa

Pseudomonas aeruginosa (n=470) isolates had susceptibility rates of 64% to meropenem (MIC_{50} 1μg/mL), 63.8% to piperacillin/tazobactam (MIC_{50} 24μg/mL), 63.4% to amikacin (MIC_{50} 4μg/mL), 58.7% to imipenem (MIC_{50} 2μg/mL), 58.3% to cefepime (MIC_{50} 6μg/mL), and 55.8% to ceftazidime (MIC_{50} 4μg/mL). Tobramycin, gentamicin and ciprofloxacin presented susceptibility rates < 55%.

Susceptibility of *P. aeruginosa* per center is described in Table 5, with susceptibility rates shown for all 20 hospital units.

E. coli

E. coli (n=288) isolates were susceptible to both imipenem and meropenem (MIC_{90} 0.19 and 0.016μg/mL, respectively), with susceptibility rates of 98.6% to piperacillin/tazobactam and amikacin, and 95.1% to ceftazidime. On the other hand, ciprofloxacin had a 76.7% susceptibility rate. Forty-two (14.6%) isolates presented MICs of ≥2 mg/mL towards the cephalosporins and were submitted to a double-disk synergy test, which suggested production of ESBL. The frequency of ESBL producers varied greatly among centers, ranging from 0 to 83.3%.

K. pneumoniae

Both carbapenems, imipenem and meropenem, presented 99.2% susceptibility rates against the *K. pneumoniae* (n=262) isolates (MIC_{90} 0.19 and 0.032μg/mL, respectively). The susceptibility rate to piperacillin/tazobactam was 87% (MIC_{90} 32μg/mL) and to 81.7% amikacin (MIC_{90} 32μg/mL). All other drugs presented susceptibility rates below 65%. ESBL production rate among *K. pneumoniae* was 51.9%. Two strains yielded MICs in the intermediate and resistant range to meropenem. These isolates were both in the intermediate MIC range for imipenem. The isolates were forwarded for more detailed molecular analysis. The ESBL production rates among *K. pneumoniae* by centers showed frequencies ranging from 0% to 100%.

Acitenobacter baumannii

Both carbapenems, imipenem and meropenem, presented 97.1% susceptibility rates against the *A. baumannii* (n=137) isolates evaluated (MIC_{50} 0.75 and 1μg/mL, respectively and MIC_{90} 2μg/mL for both). The susceptibility rate to tobramycin was 73% (MIC_{50} 1.5μg/mL and MIC_{90} 256μg/mL). All other drugs gave susceptibility rates below 55%.

Other Enterobacteriaceae

When other *Enterobacteriaceae* were examined, both carbapenems (imipenem and

Table 1. Number of isolates (n) and contribution (%) per center – MYSTIC Program Brazil 2003

Center	N	%
1	97	6.3
2	55	3.5
4	83	5.3
5	65	4.2
6	59	3.8
7	86	5.5
8	74	4.8
9	100	6.5
10	43	2.8
11	100	6.5
12	77	5.0
13	116	7.5
14	96	6.2
15	53	3.4
16	118	7.6
17	42	2.7
18	100	6.5
19	98	6.3
20	35	2.3
Total	**1,550**	**100**

Table 2. Prevalence of microorganisms isolated

Microorganism	N	%
P. aeruginosa	470	30.3
E. coli	288	18.6
K. pneumoniae	262	16.9
A. baumannii	137	8.8
E. cloacae	110	7.1
P. mirabilis	51	3.3
S. maltophilia	42	2.7
S. marcescens	38	2.5
E. aerogenes	23	1.5
C. freundii	21	1.3
K. oxytoca	12	0.8
M. morganii	12	0.8
Others	84	5.4
Total	**1,550**	**100**

Table 3. Frequency of microorganisms per main sample source

	N (%)			
Microorganism	**Blood/Catheter**	**Respiratory tract**	**Urinary tract**	**Skin/Soft tissue**
P. aeruginosa	116 (28.5)	121 (45.7)	106 (21.9)	48 (36.9)
E. coli	32 (7.9)	17 (6.4)	162 (33.5)	23 (17.7)
K. pneumoniae	70 (17.2)	32 (12.0)	90 (18.6)	15 (11.5)
A. baumannii	68 (16.7)	24 (9.1)	23 (4.8)	10 (7.7)
E. cloacae	33 (8.1)	12 (4.5)	40 (8.3)	7 (5.4)
P. mirabilis	12 (2.9)	4 (1.5)	24 (5.0)	4 (3.1)
Others	76 (18.7)	55 (20.8)	38 (7.9)	23 (17.7)
Total	**407 (100)**	**265 (100)**	**483 (100)**	**130 (100)**

Table 4. Susceptibility pattern of *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and *A. baumannii* – MYSTIC Program Brazil 2003

	%			μg/mL	
Species/antimicrobial	**S**	**I**	**R**	**MIC_{50}**	**MIC_{90}**
***P. aeruginosa* (n = 470)**					
Cefepime	58.3	11.7	30	6	>256
Ceftazidime	55.8	5.5	36	4	>256
Imipenem	58.7	4.7	36.6	2	>32
Meropenem	64	2.1	33.9	1	>32
Piperacillin/tazobactam	63.8	0	36.2	24	>256
Ciprofloxacin	49.6	2.1	48.3	1.5	>32
Gentamicin	53.2	2.5	44.3	4	>256
Tobramycin	54	4	42	1.5	>256
Amikacin	63.4	2.8	33.8	4	>256
***E. coli* (n = 288)**					
Cefepime	85.4	0	14.6	0.032	6
Ceftazidime	85.4	0	14.6	0.19	3
Cefotaxime	85.4	0	14.6	0.064	64
Imipenem	100	0	0	0.19	0.25
Meropenem	100	0	0	0.016	0.032
Piperacillin/tazobactam	98.6	1	0.4	2	4
Ciprofloxacin	76.7	2.1	21.2	0.006	>32
Gentamicin	88.2	2.8	9	0.5	8
Tobramycin	88.9	3.5	7.6	0.75	8
Amikacin	98.6	0	1.4	1.5	3
***K. pneumoniae* (n = 262)**					
Cefepime	48.1	0	51.9	1	48
Ceftazidime	48.1	0	51.9	1	48
Cefotaxime	48.1	0	51.9	4	>256
Imipenem	99.2	0.8	0	0.19	0.25
Meropenem	99.2	0.4	0.4	0.032	0.094
Piperacillin/tazobactam	87	5.7	7.3	4	32
Ciprofloxacin	64.1	5.7	30.2	0.125	>32
Gentamicin	52.3	13.4	34.3	2	128
Tobramycin	53	11.5	35.5	3	48
Amikacin	81.7	11.8	6.5	2	32
***A. baumannii* (n = 137)**					
Cefepime	33.6	19.7	46.7	24	>256
Ceftazidime	31.4	9.5	59.1	64	>256
Imipenem	97.1	0	2.9	0.75	2
Meropenem	97.1	0	2.9	1	2
Piperacillin/tazobactam	32.1	12.4	55.5	256	>256
Ciprofloxacin	34.3	0	65.7	>32	>32
Gentamicin	53.3	19	27.7	4	>256
Tobramycin	73	9.5	17.5	1.5	256
Amikacin	36.5	5.8	57.7	128	>256

Table 5. Susceptibility (%) of *P. aeruginosa* isolates per center – MYSTIC Program Brazil 2003

		% Susceptible								
Center	**n**	**CEP**	**CAZ**	**IMP**	**MEM**	**PTZ**	**CIP**	**GM**	**TB**	**AK**
1	40	12.5	12.5	10	12.5	35	10	12.5	10	32.5
2	17	94.1	94.1	88.2	94.1	94.1	88.2	88.2	88.2	88.2
4	21	66.7	66.7	61.9	66.7	66.7	61.9	57.1	61.9	61.9
5	26	50	50	19.2	42.3	46.2	19.2	23.1	23.1	57.7
6	19	52.6	47.4	52.6	52.6	47.4	31.6	57.9	52.6	52.6
7	23	56.5	39.1	69.6	69.6	47.8	56.5	56.5	56.5	60.9
8	28	50	60.7	53.5	57.1	60.7	46.4	67.9	78.6	78.6
9	25	68	68	76	76	64	60	64	60	64
10	10	100	80	100	100	90	70	70	70	90
11	16	87.5	87.5	93.8	100	100	93.8	81.3	87.5	100
12	40	60	60	60	70	65	45	57.5	50	60
13	63	69.8	71.4	71.4	76.2	73	69.8	68.3	71.4	73
14	22	31.8	31.8	50	50	54.5	22.7	22.7	22.7	36.4
15	7*	28.6	14.3	28.6	28.6	42.9	14.3	14.3	28.6	28.6
16	43	62.8	55.8	58.1	62.8	65.1	53.5	53.5	55.8	72.1
17	14	57.1	57.1	71.4	71.4	78.6	71.4	71.4	71.4	71.4
18	15	40	100	93.3	93.3	60	33.3	40	40	53.3
19	17	52.9	52.9	47.1	52.9	70.6	47.1	47.1	47.1	64.7
20	5*	60	40	40	40	40	0	0	0	0
21	19	94.7	94.7	68.4	89.5	89.5	68.4	73.7	78.9	78.9
Total	**470**	**58.3**	**58.5**	**58.7**	**64**	**63.8**	**49.6**	**53.2**	**54**	**63.4**

CEP	Cefepime	IMP	Imipenem	PTZ	Piperacillin/tazobactam
CAZ	Ceftazidime	MEM	Meropenem	CIP	Ciprofloxacin
GM	Getamicin	TB	Tobramycin	AK	Amikacin.

meropenem) gave 100% susceptibility rates against isolates of *Citrobacter* spp., *Enterobacter* spp., *Serratia* spp., *and Providencia* spp. Among *Citrobacter freundii* isolates, 52% (11/21) presented resistance to extended-spectrum cephalosporins, with a phenotype suggestive of a chromosomal AmpC hyperproducer. Among *E. cloacae* (n=110) isolates, 42 (38%) presented resistance to extended-spectrum cephalosporins, with a phenotype suggestive of chromosomal AmpC hyperproducer. Additionally, 27 of those 42 presented resistance to cefepime, also suggesting ESBL production. Among *Enterobacter aerogenes* (n=23) isolates, 7 (30%) were consistent with a phenotype of AmpC hyperproduction, and 3 (13%) of those were also suggestive of ESBL production. Among *Serratia marcescens* (n=38) isolates, 12 (32%) were consistent with a phenotype of AmpC hyperproduction, and 4 (11%) of those were also suggestive of ESBL production. Among *Proteus mirabilis* (n=51) and *Morganella morganii* (n=12) isolates, 11 (22%) and 3 (25%), respectively, presented phenotypes suggestive of ESBL production, conferring resistance to third and fourth generation cephalosporins.

Discussion

The MYSTIC Program is a large-scale surveillance program of nosocomial bacterial isolates with associated information on their MICs. Our data was collected from patients hospitalized in 20 hospitals located in eight Brazilian states during the 2003 edition of the program. The program's main objective was to evaluate the susceptibility pattern of Gram-negative bacilli isolated from patients with 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 to 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 the most frequently submitted isolate, accounting for 30.3% of all isolates, followed by *E. coli* (18.6%), *K. pneumoniae* (16.9%), *A. baumannii* (8.8%), and *E. cloacae* (7.1%). The frequency of *P. aeruginosa* and *A. baumannii* has risen significantly, when compared to the first MYSTIC edition in Brazil [18], but it has remained rather constant since the previous editions in 2001 [19] and 2002 (in press). Even with the increase in participating centers as compared to the 2001 and 2002 editions, the frequency of *P. aeruginosa* isolates has remained constant at around 30%. This may be due to the characteristics of the participating centers, which may be similar, and to the exclusive isolation of Gram-negative bacteria during all three years. It should also be noted that, similar to the previous edition, at least 57.4% of samples in the present edition were from clinically significant sources and definitely related to the infectious process (blood, catheter and urinary tract). However, 17.1% of samples were from the respiratory tract, although always considered by investigators as causative agents of the infectious processes. Nevertheless, one cannot completely rule out the contribution of colonizers as part of the total amount of isolates. The higher number of isolates from blood/catheter was expected, since our study did not aim at establishing the prevalence of nosocomial infections. But rather, the study aimed at isolating clinically-significant bacteria causative of the infectious processes.

The susceptibility patterns detected by the MYSTIC Program 2003, particularly for meropenem against *P. aeruginosa* and *A. baumannii*, in these 20 Brazilian centers demonstrated resistance rates somewhat higher than the ones determined by other studies [4,6,7,12,20,21], although lower than the ones detected in the 2002 program. The present MYSTIC edition in Brazil showed 36% resistance rate to meropenem in *P. aeruginosa* isolates, while the previous 2002 edition showed 40.2% (in press), and the others showed resistance rates to carbapenems in *P. aeruginosa* and *A. baumannii* ranging between 18-21% and 14-15%, respectively [18,19]. Possible reasons for the higher resistance patterns observed during 2002 and 2003, when compared to other editions and to other surveillances, could be based on the program's selection of carbapenem user hospital units and of specialized centers, particularly with an increased number of intensive care units during 2003. Other possible reasons could also be that the centers, although scattered around the country, were all major reference hospitals with specialized units. This may reflect a specific influence of demographic characteristics of these units in the high resistance rates obtained. Furthermore, clonal spread among *P. aeruginosa* and *A. baumannii* was confirmed during the 2002 program edition, with documented clonal spread within the same centers and among different centers, even in different city locations [22,23].

Pseudomonas aeruginosa (n=470) isolates presented high resistance rates against all antimicrobials, with descending order of susceptibility rates of 64% to meropenem (MIC_{50} 1μg/mL), 63.8% to piperacillin/tazobactam (MIC_{50} 24μg/mL), 63.4% to amikacin (MIC_{50} 4μg/mL), 58.7% to imipenem (MIC_{50} 2μg/mL), 58.3% to cefepime (MIC_{50} 6μg/mL), and 55.8% to ceftazidime (MIC_{50} 4μg/mL). Significant differences in resistance rates were observed among the centers from different regions, but in our analysis it was not

possible to identify an underlying spatial pattern. Thus one cannot say if the resistance patterns to most antimicrobials are actually spatially random, as they appear to be. Susceptibility of *P. aeruginosa* varied greatly among centers, with rates ranging from 90% to 100% S for carbapenems and piperacillin/tazobactam in centers 2, 10 and 11 to < 55% for all antimicrobials in centers 1, 5 and 14. As previously discussed, clonal spread may have contributed to the susceptibility observed in specific centers.

On the other hand, *A. baumannii* (n=137) isolates presented susceptibility rates to imipenem and meropenem of 97.1% (MIC_{50} 0.75 and 1μg/mL, respectively and MIC_{90} 2μg/mL for both), and 73% to tobramycin (MIC_{50} 1.5 μg/mL), which is in accordance with previous MYSTIC editions in the country (18, 19). *E. coli* ESBL producing isolates (14.6%) presented a similar prevalence, when compared to the 2002 edition (13.7%) and to other previous editions of the study [19,20]. Among these 42 isolates with MICs ≥ 2μg/mL towards the cephalosporins and confirmed as ESBL producers, the results of the screening showed that cefotaxime was a highly-sensitive agent for this screening. This finding suggests the predominance of CTX enzymes in Brazil.

Klebsiella pneumoniae ESBL-producing isolates (51.9%) had a higher prevalence when compared to the 2002 edition (37.7%) and lower than the 2001 edition (63.5%) [18]. Similar to *E. coli*, cefotaxime was also the most sensitive ESBL screening agent. A tendency analysis will be reported separately. However, some factors may have contributed to the observed variation, particularly in the rates of *K. pneumoniae* ESBL-producing isolates. Clonal spread involving *K. pneumoniae* ESBL-producing isolates cannot be ruled out within and among participating centers, contributing to the observed rates. Nevertheless, one cannot exclude the possibility of a selection bias in the samples, since ours was not a prevalence defining study. Two strains yielded MICs in the intermediate resistance range to meropenem. These isolates were both in the intermediate MIC range for imipenem. The isolates were sent out for more detailed molecular analysis.

In conclusion, resistance development to antimicrobials is currently a major concern for the medical community worldwide, since infections caused by resistant bacteria seem to be associated with worsened morbidity factors (hospitalization, death and illnesses rates) [24]. The implementation of monitoring programs is an important part of the prevention strategy against the progression of resistance. Surveillance in specific units apparently offers a unique opportunity to detect the emergence of resistance in bacteria used as sentinel agents, especially in units with higher antibiotic usage density [1,25]. Our study confirms previous findings that carbapenem resistance among Enterobacteriacea is still rare in the region [4,6,7,12,18,19,21-23]. On the other hand, *A. baumannii* and *P. aeruginosa* have been 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, as determined by this and other studies [6,7,12,18,19,21-23], added to the facts that they did not present high susceptibility rates to any of the drugs, and because no single regimen had a high target attainment on a Monte Carlo simulation program based on the similar data [26], the use of empirical combination therapy to treat these pathogens may be justified in selected centers (i.e. those with high resistance rates to carbapenems).

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