

COST OF ANTIMICROBIAL TREATMENT IN PATIENTS INFECTED WITH MULTIDRUG-RESISTANT ORGANISMS
IN THE INTENSIVE CARE UNIT

FABIANA XAVIER CARTAXO SALGADO¹, JULIANA CARNEIRO GONÇALVES², CARLA MONTEIRO DE SOUZA²,
NORIBERTO BARBOSA DA SILVA³, TARQUINO E. GAVILANES SANCHEZ¹,
MARGÔ GOMES DE OLIVEIRA KARNIKOWSKI²

¹*Departamento de Controle de Infecção Hospitalar, Hospital Regional da Asa Norte, Brasília,*

²*Universidade de Brasília, ³Universidade Católica de Brasília, Brasil*

Abstract This study aims to compare the costs of antimicrobial drugs used in the treatment of patients infected with multidrug-resistant organisms (MDRO) or those not infected with this type of organisms in an intensive care unit (ICU). It is a retrospective comparative case-control study, performed in a public hospital in the capital city of Brazil, comprising the years 2007, 2008 and 2009. Information on age, sex, length of hospitalization, clinical outcome, antimicrobial drugs, microorganisms and microbial sensitivity to antibiotics was collected. Spearman and Mann-Whitney tests were used for statistical analysis. The level of significance was set at $p < 0.05$. The sample consisted of 401 patients with a mean age of 51.36 years (± 19.68) being 226 (56.4%) male. As for the length of stay, 32.9% of the patients remained more than 20 days, with 195 discharged and 206 deaths. Global cost of antimicrobial treatment was US\$ 1113 221.55 during the three year period. Treatment cost for patients with MDRO was higher than for those without ($p = 0.010$). At least one MDR strain was isolated in 54.6% of the patients. According to these results, nosocomial infections due to MDRO and the high costs involved may endanger the effectiveness of antimicrobial therapy in ICU and Health Centers.

Key words: antimicrobial drugs, costs, multidrug-resistant organisms, ICU

Resumen **Costo de la terapia antimicrobiana en pacientes infectados con microorganismos multiresistentes en la Unidad de Cuidados Intensivos.** El presente estudio tuvo como objetivo comparar los costos del tratamiento con fármacos antimicrobianos para las infecciones debidas a organismos multiresistentes (OMDR) *versus* aquellas debidas a gérmenes no multiresistentes, en la Unidad de Cuidados Intensivos (UCI) de un hospital público de Brasília, Distrito Federal. Fue un estudio retrospectivo, de casos y controles y abarcó un período de tres años (2007, 2008, 2009). Se recolectó información sobre edad, sexo, tiempo de internación, resultados clínicos, antimicrobianos usados, microorganismos aislados y su sensibilidad a los antibióticos. Se utilizaron en el análisis estadístico las pruebas de Spearman y de Mann-Whitney, con $p < 0.05$. La muestra consistió en 401 pacientes con media de edad de 51.36 años (± 19.68), siendo 226 varones (56.4%). En cuanto al tiempo de internación, un 32.9% de los pacientes permanecieron más de 20 días, con 195 altas y 206 óbitos. El tratamiento antimicrobiano costó US\$ 1113 221.55 en los tres años, siendo éste mayor para los que presentaron OMDR que para los que no los presentaron ($p = 0.01$). Se comprobó la presencia de, por lo menos, un microorganismo multiresistente en el 54.6% de los pacientes. La infección intrahospitalaria con OMDR y el elevado costo del tratamiento de los pacientes infectados con estos microorganismos puede comprometer la efectividad de la terapia antimicrobiana en estas Unidades y Centros de Salud.

Palabras clave: antimicrobianos, costos, microorganismos multiresistentes, UCI

The costs of health care services have risen in the last decades as a result of changes in the age distribution of the population, the expanding levels of health care provision and more sophisticated medical techniques^{1,2}.

Patients in intensive care units (ICU) often present infectious complications with high mortality rates and increased costs. In developed countries, such as the US and Canada, intensive care medicine has been, for years, the major source of hospital costs³.

Antimicrobial drugs are basic components to fight infections in critically ill patients and, due to resistance that microorganisms develop against this class of drugs, they create an additional source of cost in ICU.

Over 50% of the infections associated with health care settings are caused by resistant strains⁴, particularly multidrug-resistant organisms (MDRO), such as

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Postal Address: Msc. Fabiana Salgado, Secretaria de Estado de Saúde do Distrito Federal, Departamento de Controle de Infecção Hospitalar do Hospital Regional da Asa Norte, Brasília, QR 122 Conjunto 13 Casa 06, Samambaia Sul, Distrito Federal, Brasil
Fax (55-061) 33568435 e-mail: fabianacartaxo@yahoo.com.br

methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacter sp.*, *Klebsiella pneumoniae*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and, more recently, *Escherichia coli*⁵⁻⁷.

Therefore, nosocomial infections, particularly those caused by MDRO, have become more prevalent, which may affect the efficacy of treatments and substantially increase costs for the health system^{8,9}.

Some of the relevant factors implicated in the increase of nosocomial multidrug resistance are lengthy hospitalizations, lack of resources for nosocomial infection prevention and surveillance programs, use of diverse invasive diagnostic and therapeutic procedures, and the indiscriminate use of antimicrobial drugs both in the community and in hospitals¹⁰. In Brazil, the massive and indiscriminate use of antimicrobial drugs has led health surveillance authorities to suggest the adoption of urgent measures to prevent the appearance of new multidrug-resistant strains¹¹.

The treatment of infections in hospitalized patients has high costs in the US as well as in Latin American and European countries, and multidrug resistance tends to further increase costs⁹⁻¹².

Few studies about the cost of drugs have evaluated the effect of microbial multidrug resistance on antimicrobial costs, particularly in the ICU.

This study compared the costs of treatment with antimicrobial drugs for patients infected or not infected with multidrug-resistant organisms in an intensive care unit.

Materials and Methods

This retrospective comparative case-control study was conducted in the ICU of a public hospital in the capital city of Brazil. Our investigation was designed as a case-control study because it compares patients who have been infected with MDRO with patients with similar characteristics who have not been infected with this type of organisms. The ICU has 10 beds for clinical and surgery patients aged ≥ 14 years, and is located in one of the largest public hospitals in the Federal District. The hospital has 359 beds and provides health care for patients covered by the Brazilian Unified Health System.

Patients interned in the ICU in three years: 2007, 2008 and 2009, were included if they had received antimicrobial drugs and remained hospitalized for more than 24 hours, were 14 years or older, regardless of sex, underlying disease or comorbidities at the time they were enrolled in the study. Those patients who had negative results in all microbiological tests for presence of microorganisms, or had positive results for bacterial infection, but antibiotic sensitivity test (AST) results were not available were excluded from the study.

Data about sex, age, length of stay, clinical outcome and antimicrobial drugs used were collected from medical charts. Antimicrobial drugs were recorded using their names in the Brazilian Nomenclature (*Denominação Comum Brasileira*),

and costs were evaluated according to the prices paid by the State Health Department of *Distrito Federal*. The financial values here provided have been converted to the US dollar according to its average value during 2007, 2008 and 2009, based on the exchange rate provided by the Central Bank of Brazil. To calculate cost for each antimicrobial drug, the cost of a daily dose in grams was multiplied by the number of days that the drug has been administered.

The identification of microorganisms, as well as data about antimicrobial sensitivity, were obtained from the hospital microbiology laboratory where samples were processed using an automated Walkway unit (MicroScah, Siemens) and analyzed according to guidelines issued by the National Committee for Clinical Laboratory Standards (NCLS)¹³, and antibiotic sensitivity tests in the case of bacteria¹⁴.

Microbial multidrug resistance was defined when a bacterial strain was resistant to two or more antibiotic classes to which it was intrinsically susceptible¹⁵. The variables sex, age, clinical outcome, length of stay, cost, antimicrobial drugs used and number of MDRO were described as percentages, frequency, mean and standard deviation¹⁶⁻¹⁸.

The PASW Statistics¹⁹ software (SPSS Inc.) was used for all statistical analyses. After exploratory analysis, the Kolmogorov-Smirnov skewness and normality tests were used if the variables cost, number of MDRO and length of stay were not normally distributed.

The variables sex, age, clinical outcome, length of stay, cost, antimicrobial drugs used and number of MDRO were described as percentage, frequency, mean and standard deviation.

The Spearman test was used to evaluate possible associations between cost and length of stay, number of MDRO and length of stay, and cost and number of MDRO. The Mann-Whitney test was used to evaluate whether there was a significant difference in cost of each antimicrobial drug between the group with multidrug resistance and the group without it. The level of significance was set at $p < 0.05$, and the confidence interval, at 95%.

Results

Of the 401 patients included in the study [226 (54.36%) men; mean age: 51.36 ± 19.68 years], 3.91% were hospitalized for 20 days or longer. The analysis of clinical outcome revealed that 195 (4.63%) were discharged and 206 (54.37%) died during the period of this study.

In the samples collected from the ICU patients, 697 pathogens were detected at a mean 2.5 ± 1.83 organism per patient: 575 (82.4%) were bacteria, and 122 (17.6%), fungi. Twelve different bacterial species were identified among these 697 pathogen isolates, 357 (62%) were Gram negative, and 218 (38%), Gram positive. The most prevalent were *Staphylococcus* ($n = 173$), *Acinetobacter* ($n = 107$), *Pseudomonas* ($n = 91$), *Enterobacter* ($n = 55$), *Klebsiella* ($n = 50$), *Enterococcus* ($n = 43$) and *Escherichia* ($n = 19$). Among the fungi predominated *Candida tropicalis* ($n = 42$), *Candida albicans* ($n = 27$), yeasts ($n = 19$), *Candida sp* ($n = 12$), *Candida glabrata* ($n = 8$), *Candida parapsilosis* ($n = 6$) and others ($n = 6$).

At least one MDRO was found in 219 individuals, which represented 54.6% of the analyzed population. *Acinetobacter baumannii* ($n = 99$) was the most prevalent,

found in 7.52% of the samples, followed by *Pseudomonas aeruginosa* (n = 86; 6876%), *Klebsiella pneumoniae* (n = 42; 5.12%), *Staphylococcus aureus* (n = 60; 52%), *Enterobacter aerogenes* (n = 26; 6656%), *Enterococcus faecalis* (n = 21; 7.6%), *Enterobacter cloacae* (n = 24; 4328%), *Enterococcus faecium* (n = 15; 2328%) and *Escherichia coli* (n = 19; 46.2%).

The total cost of antimicrobial treatment for all patients was US\$ 1113 221.55 along three years. Patients with MDRO had a greater total cost than patients without it (p = 0.010). The classes of antimicrobial drugs most often prescribed were carbapenems (n = 332), antifungal agents (n = 208) and oxazolidinones (n = 202) for patients with or without MDRO infection (Table 1).

TABLE 1.– Antimicrobial treatment of patients with and without multidrug-resistant organisms (MDRO) infection hospitalized in an Intensive Care Unit. Comparison of costs.

Antimicrobial agent	Patients without MDRO (n = 182)		Patients with MDRO (n = 219)		p
	N° prescriptions	cost (US\$)	N° prescriptions	cost (US\$)	
<i>Aminoglycosides</i>					
Amikacin	2	14.1	23	140.00	0.427
Gentamicin	1	0.41	11	26.4	0.332
<i>β-lactamase inhibitors</i>					
Ampicillin-sulbactam	23	2 030.32	28	2 083.93	0.495
Piperacillin-tazobactam	44	4 606.99	80	11 464.41	0.754
Oxacillin	4	148.88	0	0.00	-
<i>Cephalosporins</i>					
Cefazolin	4	19.22	2	15.66	0.800
Ceftazidime	0	0.00	2	67.59	-
Ceftriaxone	6	31.60	18	174.18	0.537
Cefepime	56	3 351.13	81	4 394.16	0.610
<i>Quinolones</i>					
Ciprofloxacin	16	996.07	28	2 790.78	0.660
Levofloxacin	7	1 092.53	17	7 591.06	0.260
<i>Lincosamide</i>					
Clindamycin	40	453.31	69	992.95	0.355
<i>Carbapenems</i>					
Imipenem	73	30 411.99	104	47 011.94	0.527
Meropenem	36	21 219.43	101	85 891.28	0.029
Ertapenem sodium	8	4 685.68	10	7 790.43	0.408
<i>Sulfonamides</i>					
Trimethoprim-sulfamethoxazole	9	226.52	18	421.39	0.743
<i>Glycopeptides</i>					
Vancomycin	28	1 835.69	47	3 740.68	0.308
Teicoplanin	5	1 297.19	5	1 259.92	0.690
<i>Oxazolidinone</i>					
Linezolid	68	105 800.85	134	308 795.41	0.000
<i>Antifungal agents</i>					
Fluconazole	54	21 565.60	97	53 919.85	0.108
Caspofungin acetate	9	43 047.50	28	236 720.72	0.048
Amphotericin B.	3	6 580.31	8	16 976.47	0.921
Voriconazole	4	10 164.21	5	23 192.16	0.556
<i>Others</i>					
Tigecycline	0	0.00	2	3 906.25	-
Polymyxin B	0	0.00	8	1 212.06	-
Colistimethate sodium	2	1 851.02	15	18 582.72	1.000
Azithromycin	17	5 812.64	14	5 173.29	0.830
Metronidazole	28	692.63	31	964.17	0.169
Total	545	267 921.70	986	845 299.85	0.010

The analysis of antibiotic prescriptions revealed that 694 (45.3%) were for broad-spectrum antibiotics at a cost of US\$ 233 766.52, which accounted for 21% of the total cost of antimicrobial drugs. The analysis of broad-spectrum antimicrobial drugs showed that US\$ 166 468.97 were spent to treat patients with MDRO infections, and US\$ 67 429.66, for patients without MDRO infection.

There was a significant correlation between the number of MDRO, costs ($p \leq 0.010$) and length of stay ($p \leq 0.010$), as well as a positive correlation between length of stay and cost ($p \leq 0.010$).

The analysis of cost for antimicrobial treatment of patients discharged due to clinical improvement revealed that those without MDRO infection ($n = 94$) spent US\$ 106 255.65, whereas the cost for those with MDRO infections ($n = 101$) was \$ 374 492.44. Of the patients who died, those 88 without MDRO infection had a total antimicrobial treatment cost of US\$ 161 338.42, whereas for those 118 with MDRO infection the expenditure was US\$ 471 135.03. A total of US\$ 632 473.45 were spent on antimicrobial agents for patients who later died, what accounted for 56.8% of total expenses.

Discussion

Infections in general complicate the health conditions of hospitalized patients, particularly in the ICU, and generate high costs for the health care sector^{9, 15-18}. This study confirmed the high cost of antimicrobial agents per infected patient, particularly in cases where the pathogen was a MDRO. Nevertheless, some values here reported may be underestimated because only the antimicrobial doses administered were included. Additional costs due to preparation of injectable drugs and other pharmacy materials used in the process, as well as workload costs, which might further increase treatment costs in Brazilian ICUs, were not included here⁵. The amounts of money spent in the antimicrobial treatment of patients with MDRO infections have been shown to be greater than those expenses involved in the treatment of non MDRO infections. This is especially valid for certain strains, such as *Acinetobacter baumannii*^{9, 19} and *Pseudomonas aeruginosa*²⁰⁻²², which corroborates our findings.

Several studies conducted in developed countries showed, as in our study, that patients with MDRO infections have a longer hospital stay, higher mortality rates, and greater costs than patients with infections due to sensitive strains^{9, 19-23}. These results confirm the relevance of both reducing the length of ICU stay and reinforcing intra-hospital infection prevention measures.

Length of hospitalization has an important role in the economic burden, both in cases of infectious complications and in other clinical events. When hospitalization time is associated with MDRO infection, costs are usually higher:

in the US, they range from US\$ 6 000 to 30 000, and in Guatemala, from US\$ 900 to 9 800 in the group of patients with hospital-acquired MDRO infection^{8, 24}.

The analysis of antimicrobial agents here prescribed showed that these are quite similar than those described in the literature²⁵⁻²⁷ and revealed a high use of broad-spectrum drugs, advanced resources in pharmaceutical innovation and potential treatment efficacy, although with heavy cost.

It was also found that expenses due to antimicrobial drugs for the group of patients that later died was about 3 times greater than those for the treatment of patients that later were discharged due to clinical improvement. This difference was valid either for patients with or without MDRO infection. This is a concerning finding because it compromises the use of resources in health care for treatments that do not achieve the expected results, that is, to save the patient's life.

Only three drugs accounted for a significant difference in costs when patients with and without MDRO infection were compared. This finding suggests that careful attention was not paid to the rational prescription of antimicrobial agents, which is universally understood to be one of the major steps to control microbial resistance.

The consequences for individual and collective health and the economic impact of multidrug resistance draw attention to the importance of making wise use of the financial resources earmarked for health care, which represent a small percentage of the gross national product in developing countries, particularly in Brazil.

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Las lenguas siguen la marcha de los progresos y de las ideas: pensar fijarlas en un punto dado, a fuer de escribir castizo, es intentar imposibles [...]. El que una voz no sea castellana es para nosotros objeci n de poqu sima importancia: en ninguna parte hemos encontrado todav a el pacto que ha hecho el hombre con la divinidad ni con la naturaleza, de usar tal o cu al combinaci n de s labas para entenderse: desde el momento que por mutuo acuerdo una palabra se entiende, ya es buena. [...], no queremos esa literatura reducida a las galas del decir, que concede todo a la expresi n y nada a la idea, sino una literatura hija de la expresi n y de la historia, pens ndolo todo, diciendo todo en prosa, [...] literatura nueva, expresi n de la sociedad nueva que constituimos. [...]. Libertad en literatura como en las artes, como en la industria, como en la conciencia.

Domingo F. Sarmiento

En: *Pol mica Literaria*. Buenos Aires: Editorial Cartago, 1955, p 82-3