Economic burden of inpatients infected with *Klebsiella pneumoniae carbapenemase*

Impacto econômico do tratamento de pacientes infectados com *Klebsiella pneumoniae carbapenemase*

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❚ **ABSTRACT**

Objective: To estimate the direct medical costs of drug therapy of *Klebsiella pneumoniae carbapenemase* (KPC) infection patients in hospital-based context. **Methods:** A cost-of-illness study conducted with a prospective cohort design with hospitalized adults infected by KPC. Data collection was performed using an instrument composed of sociodemographic data, clinical and prescription medication. Estimates of the direct costs associated to each treatment were derived from the payer's perspective, in the case of federal public hospitals from Brazil, and included only drug costs. These costs were based on the average price available at the Brazilian Price Database Health. No discount rate was used for the cost of drugs. The costs are calculate in American Dollar (US$). **Results:** A total of 120 inpatients participated of this study. The total drug cost of these inpatients was US$ 367,680.85. The systemic antimicrobial group was responsible for 59.5% of total costs. The direct drug cost per patients infected by KPC was conservatively estimated at nearly US$ 4,100.00, and about of 60% of costs occurred during the period of infection. **Conclusion:** The findings of our study indicate a thoughtful economic hazard posed by KPC that all healthcare sectors have to face. The increasing worldwide incidence of these bacteria represents a growing burden that most health systems are unable to deal with. There is an imperative need to develop protocols and new antimicrobials to treatment of KPC, aiming to rearrange resources to increase the effectiveness of healthcare services.

Keywords: *Gram*-negative bacteria; *Enterobacteriaceae*; *Klebsiella*; *Klebsiella pneumoniae*; Costs and cost analysis; Health care economics and organizations; Drug therapy; Health expenditures; Anti-infective agents

❚ **RESUMO**

Objetivo: Estimar os custos médicos diretos da terapia medicamentosa de pacientes com infecção por *carbapenemase* por *Klebsiella pneumoniae carbapenemase* (KPC) em contexto hospitalar. **Métodos:** Estudo de custo de doença realizado com desenho de coorte prospectiva, com adultos hospitalizados infectados por KPC. A coleta de dados foi realizada usando instrumento composto por dados sociodemográficos, medicamentos clínicos e prescritos. As estimativas dos custos diretos associados a cada tratamento foram derivadas da perspectiva dos pagadores, no caso dos hospitais públicos federais do Brasil, e incluíram apenas custos de medicamentos, os quais basearam-se no preço médio disponível na *Price Database Health* do Brasil. Nenhuma taxa de desconto foi utilizada para o custo dos medicamentos. Os custos foram calculados em dólares norte-americanos (US$). **Resultados:** Um total de 120 pacientes hospitalizados participou do estudo. O custo total da droga desses pacientes internados foi de US$ 367,680.85. O grupo antimicrobianos de uso sistêmico foi responsável por 59,5% dos custos totais. O custo

direto estimado de forma conservadora, por paciente, foi de aproximadamente US$ 4,100.00, e cerca de 60% destes se deram durante o período de infecção. **Conclusão:** Os achados deste estudo apontam um risco econômico importante relacionado a KPC, o qual todos os setores de saúde terão que enfrentar. A incidência mundial em elevação destas bactérias representa carga crescente, e a maioria dos sistemas de saúde é incapaz de resolvê-la. Há necessidade imperativa de se desenvolverem protocolos e novos antimicrobianos para o tratamento de KPC, com o objetivo de reorganizar os recursos para aumentar a efetividade dos serviços de saúde.

Descritores: Bactérias *Gram*-negativas; *Enterobacteriaceae*; *Klebsiella*; *Klebsiella pneumoniae*; Custos e análise de custo; Economia e organizações de saúde; Tratamento farmacológico; Gastos em saúde; Anti-infecciosos

INTRODUCTION

Klebsiella pneumoniae carbepemase (KPC) is a multidrug resistant bacteria, with a costly therapy and high mortality rate.[1,2] The World Health Organization (WHO) published that carbapenem-resistant *Enterobacteriaceae* has the highest level of priority that new antibiotics are urgently needed.[3] The incidence of KPC increased quickly on the last years, from 1% (2001) to 30% (2008) of all hospital infections. Cases have been reported in other regions of the world, including Europe,[4,5] Asia,[6,7] Australia,[8] and South America.[9-11]

Patients with long periods of hospitalization, mechanical ventilation, undergoing organ or stem cell transplantation, and treatment with antimicrobial agents are more likely to develop KPC infection.[12] This bacterium is involved in extra-intestinal infections, urinary tract infection, pneumoniae, bloodstream infections, surgical wound infections, endocarditis and sepsis, and the mortality can be higher than 40% in 30 days.[4,6]

The annual economic burden of multidrug resistant bacteria's amounted to more than US$ 45 billion, only considering direct and indirect costs.[13] Annually, just the pharmaceutical purchases can represent 70% of out-of-pocket health costs in India, 43% in Pakistan, and 20% in Brazil.[13] The economic cost of therapy and the high mortality rates of KPC make this infection a relevant health problem.[14-16]

This study aims to fill the gap in the scientific literature about the costs of KPC infection in the context of the Brazilian Unified Health System (SUS – *Sistema Único de Saúde*), considering the site of infection, drug class and treatment period. Moreover, it aims to promote knowledge about hospital costs of KPC infection treatment, to assist hospital service managers to estimate the economic impact and adopt cost-effective measures to prevent nosocomial infections.

OBJECTIVE

To evaluate and estimate the direct medical costs of drug therapy of *Klebsiella pneumoniae carbepemase* infection patients at hospitals, and to determine the economic impact of the infection period. Moreover, to estimate the cost of drug therapy per patient, according to site of infection and drug class.

METHODS

A cost-of-illness study was conducted with a prospective cohort design. It was carried out at the *Hospital Universitário de Santa Maria*, at Santa Maria (RS), Brazil, between March 2016 and December 2017. The study was approved by the Research Ethics Committee of the Nursing School, *Universidade de São Paulo*, under no. 1.872.201, CAAE: 61406316.7.0000.5392. The study was performed according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines.[17]

The study participants were adult inpatients with KPC infection during hospitalization, confirmed by laboratory testing. Data collection was performed using an instrument including sociodemographic data (sex, age, colour or race, marital status, and educational level), clinical data (site of infection, length of hospital stay, periods of infection, reinfection and reasons for hospital discharge) and prescription medication (drug per day, dose and route of administration). These data were obtained by accessing the participant's records after antibiogram confirming KPC. The time line was considered until patient's discharge.

The drugs were initially classified by the World Health Organization Anatomical Therapeutic Chemical (ATC) classification system, which divides substances into different groups according to the organ or system they act on and in their chemical, pharmacological and therapeutic properties. We use the fifth level of this system to identify the drugs (subgroup for chemical substance). For other analyses they were grouped according to the first level (main anatomical group), second level (main therapeutic group), third level (therapeutic/pharmacological subgroup) or fourth level (chemical/therapeutic/pharmacological subgroup).

The infection period was verified through the antibiogram to classify the treatment period in prior to infection, during infection, and after infection.

A standardized approach by the SUS was used to address treatment costs. Estimates of the associated direct costs of each treatment were derived from the payer's perspective, in the case of Public Federal Hospitals, and included only drug costs.

For the costs of drugs, all medications were included, either for treatment of infection or of comorbidities. Drug costs were based on the average price available in at *Departamento de Informática* of the SUS (DATASUS; http://bps.saude.gov.br/login.jsf), and for the study, we used the purchase prices of federal public agencies during the study period. No discount rate was used for the cost of drugs. The costs were calculated in United States Dollars (US$), using a reference of US$ 1=R$ 3,20 (Brazilian reals).

The daily cost of each drug was achieved by dividing the prescribed daily dose by the drug dosage, and then multiplied by the cost of the drug. Moreover, for the cost of the total treatment, the total number of days at hospital was added, as the formula:

$$\text{therapy daily cost} = \frac{\text{daily dose of drug y}}{\text{presentantion of drug y}} \times \text{cost of drug y}$$

The descriptive analysis was performed to present the prescribed drugs according to ATC. To verify if there is difference in the total cost according to the period of treatment and site of infection, the Kruskal-Wallis test was used. A significance level of 5% was adopted, and the analyses was made using the Statistical Package for the Social Sciences (SPSS) 21.0 software.

RESULTS

A total of 120 inpatients infected by KPC participated of this study. Of these, 60% (n=72) were male, with a mean age of 57.45 (standard derivation 19.46) years. Pardos and Indians accounted for 6.7% (n=8), most were married (40.8%), and 13.9% (n=16) were illiterate.

The main site of infection was intra-abdominal (n=65; 54.2%), followed by urinary tract (n=24; 20.0%), pneumonia (n=18; 15.0%), skin and soft tissues (n=6; 5.0%), bloodstream (n=4; 3.3%), and osteoarticular infection (n=3; 2.5%). Patients with pneumonia had the longest mean hospital stay (79.6 days), with minimum (min) of 14 days and maximum (max) of 347 days. They were followed by patients with skin and soft tissue

infections (mean of 74.0 days; min 52 days; max 105 days); urinary tract infection (mean of 65.5 days; min 15 days; max 202 days); intra-abdominal infections (mean of 56.8 days; min 7 days; max 187 days); bloodstream infection (mean of 48.8 days; min 29 days; max 83 days); and osteoarticular infection (mean of 30 days; min 21 days; 52 days).

In systemic antimicrobial group, the most often used agents were meropenem (n=1,451; 18.2%), vancomycin (n=1,045; 13.1%), amikacin (n=781; 9.8%), polymyxin B (n=631; 7.9%), metronidazole (n=561; 7.0%), piperacillin and tazobactam (n=487; 6.1%), considering the days of hospitalization.

For bloodstream infection, the more frequently used medicines were meropenem (n=71; 20.5%), sulfamethoxazole and trimethoprim (n=45; 13.0%), ampicillin (n=28; 8.1%), and ciprofloxacin (n=28; 8.1%). In intra-abdominal infection, the medicines more often used were meropenem (n=783; 19%), vancomycin (n=540; 13.1%), and amikacin (n=370; 9.0%). For urinary tract infection, the most commonly used drugs were meropenem (n=215; 16.6%), vancomycin (n=147; 11.4%), and amikacin (n=137; 10.6%). In osteoarticular infection, the drugs more often used were meropenem (n=57; 15.5%), vancomycin (n=41; 11.2%), and amikacin (n=38; 10.4%). In skin and soft tissue infections, meropenem (n=74; 20.5%), polymicyn B (n=63; 17.5%), and amikacin (n=58; 16.1%) were the drugs more often used. In pneumonia, meropenem (n=251; 17.1%), polymicyn B (n=158; 10.8%), and amikacin (n=151; 10.3%).

The mean time of initial prescription of antimicrobial was between 6 to 9 days, with a range between 2 to 25 days. Pneumonia presented a mean of 9.4 days (min 2 days; max 24 days) of initial prescription of antimicrobials, followed by intra-abdominal infection (mean 8.8 days; min 3 days; max 25 days), skin and soft tissues (mean 8.1 days; min 2 days; max 15 days), urinary tract infection (mean 7.4 days; min 2 days; max 15 days), bloodstream infection (mean 7.2 days; min 3 days; max 20 days), and osteoarticular (mean 6.1 days; min 5 days; max 9 days).

The total drug cost of these inpatients was US$ 367,680.85. The systemic antimicrobial group was responsible for 59.5% of these costs, and 19.2% were from the blood and hematopoietic organ group. Considering the systemic antimicrobial group, antimicrobial drugs for systemic use accounted for 66.5% of the total costs of this group. The antibacterial agent beta-lactam accounted for 47.3% of cost of the

systemic antimicrobial group. All economic costs of drug therapy are shown in table 1.

Three groups of drugs (systemic antimicrobials, blood and hematopoietic organs, and digestive tract and metabolism) accounted for 85% of total cost of patients, but just accounted for 21.4% of total sum of items (Table 2).

Four antimicrobials (amikacin, meropenem, polymyxin B and vancomycin) accounted for 48.6% of prescriptions of this group, whereas other antimicrobials were prescribed for less than 5 days (erythromycin, benzylpenicillin). Table 3 shows all antimicrobials prescribed

according to the period of infection, being evident the varied prescriptions for treatment of KPC infection.

The mean cost per patient was significantly (p=0.049) higher during the infection period (US$ 2,017.40; SD US$ 3,497.01), when compared to pre-infection period (US$1,169.98; SD US$ 1,863.07) and post-infection period (US$ 947.77; SD US$ 1,3693.83). Higher costs were observed during KPC infection. Only the therapeutic group of systemic antimicrobials showed significant difference in costs during the hospitalization, since the period of infection presented higher costs (Table 4).

Table 1. Cost of therapy according to drug class

Variable	Pre-infection period		Infection period		Post-infection period		Full period	
	US$	%	US$	%	US$	%	US$	%
Digestive tract and metabolism	7,202.30	3.5	13,233.09	2.8	2,576.36	4.6	23,011.78	6.3
Antimicrobials for systemic use	51,985.80	25.5	151,762.80	32.2	15,061.22	26.8	218,809.81	59.5
Antibacterial for systemic use	46,260.50	22.7	86,469.63	18.3	12,694.53	22.6	145,424.64	39.6
Aminoglycosides	193.40	0.1	898.14	0.2	167.83	0.3	1,259.41	0.3
Beta-lactams	26,703.90	13.1	36,059.01	7.6	5,962.98	10.6	68,725.87	18.7
Macrolides, lincosamides and streptogramins	1,195.00	0.6	743.14	0.2	4.30	<0.1	1,942.47	0.5
Other antibacterial								
Glycopeptide antibacterial	7,800.90	3.8	8,757.81	1.9	1,052.20	1.9	17,610.94	4.8
Imidazole derivatives	333.20	0.2	224.33	<0.1	84.40	0.2	641.94	0.2
Nitrofuran derivatives	-	-	1.70	<0.1	-	-	1.70	<0.1
Daptomycin	-	-	6,303.41	1.3	-	-	6,303.41	1.7
Linezolid	4,953.60	2.4	1,955.91	0.4	1,676.49	3.0	8,586.04	2.3
Polymyxins	4,058.80	2.0	15,514.49	3.3	2,972.72	5.3	22,545.97	6.1
Quinolone antibacterial	811.00	0.4	642.06	0.1	29.37	0.1	1,482.41	0.4
Sulfonamides and trimethoprim	210.60	0.1	268.74	0.1	163.43	0.3	642.80	0.2
Tetracycline	-	-	15,100.88	3.2	580.80	1.0	15,681.68	4.3
Antimycotics for systemic use	4,105.30	2.0	63,621.60	13.5	2,317.32	4.1	70,044.19	19.1
Antivirals for systemic use	1,571.30	0.8	1,343.18	0.3	49.37	0.1	2,963.84	0.8
Immune sera and immunoglobulins	48.80	<0.1	328.38	0.1		0.0	377.13	0.1
Antineoplastic and Immunomodulating agents	5,256.00	2.6	8,356.57	1.8	107.90	0.2	13,720.47	3.7
Antiparasitic products, insecticides and repellents	36.50	<0.1	59.73	<0.1	5.75	0.0	102.00	0.0
Blood and blood forming organs	25,580.20	12.5	37,604.44	8.0	7,509.80	13.4	70,694.39	19.2
Cardiovascular system	4,897.30	2.4	7,135.43	1.5	806.90	1.4	12,839.66	3.5
Dermatological products	178.50	0.1	122.25	<0.1	93.47	0.2	394.26	0.1
Genito-urinary system and sex hormones	98.60	<0.1	107.39	<0.1	5.81	0.0	211.83	0.1
Musculoskeletal system	542.00	0.3	2,130.31	0.5	365.10	0.7	3,037.43	0.8
Nervous system	4,402.80	2.2	7,426.60	1.6	921.78	1.6	12,751.13	3.5
Respiratory system	2,567.90	1.3	2,878.61	0.6	581.22	1.0	6,027.73	1.6
Sensory organs	1,373.10	0.7	523.94	0.1		0.0	1,897.06	0.5
Systemic hormonal preparations, excluding sex hormones and insulins	851.70	0.4	1,025.48	0.2	101.29	0.2	1,978.46	0.5
Various	662.80	0.3	1,335.52	0.3	206.53	0.4	2,204.86	0.6
Total	203,881.90		471,934.57		56,098.86		367,680.85	

Table 2. ABC curve according with Anatomical Therapeutic Chemical Group

Class	Group	Units consumed	Mean price US$	Total cost US$	Paid per group (%)	Units consumed (%)	Cumulative cost (%)
A	Anti-infective for systemic use	31,270	6.99	218,809.81	59.5	7.1	59.5
	Blood and blood forming organs	31,847	2.21	70,694.39	19.2	14.3	78.7
	Alimentary tract and metabolism	36,054	0.63	23,011.78	6.3	21.4	85.0
B	Antineoplastic and immunomodulating agents	616	22.28	13,720.47	3.7	28.6	88.7
	Cardiovascular system	25,251	0.50	12,839.66	3.5	35.7	92.2
	Nervous system	46,747	0.27	12,751.13	3.5	42.9	95.7
C	Respiratory system	3,696	1.63	6,027.73	1.6	50.0	97.3
	Musculoskeletal system	916	3.31	3,037.43	0.8	57.1	98.2
	Various	1,000	2.20	2,204.86	0.6	64.3	98.8
	Systemic hormonal preparations, excluding sex hormones and insulins	4,387	0.45	1,978.46	0.5	71.4	99.3
	Sensory organs	721	2.63	1,897.06	0.5	78.6	99.8
	Dermatological products	294	1.34	394.26	0.1	85.7	99.9
	Genito-urinary system and sex hormones	406	0.52	211.81	<0.1	92.9	99.9
	Antiparasitic products, insecticides and repellents	338	0.30	102,009.13	<0.1	100.0	100.0

Table 3. Prescribed days of drug therapy according to medication of the therapeutic systemic antibacterial subgroup

Antimicrobial	Pre-infection period n (%)	Infection period n (%)	Post-infection period n (%)	Full period n (%)
Amikacin	80 (2.6)	546 (13.8)	93 (13.1)	719 (9.2)
Amoxicillin	99 (3.2)	71 (1.8)	8 (1.1)	178 (2.3)
Ampicillin	28 (0.9)	22 (0.6)	14 (2.0)	64 (0.8)
Ampicillin, combinations	87 (2.8)	99 (2.5)	23 (3.2)	209 (2.7)
Azithromycin	30 (1.0)	12 (0.3)	-	42 (0.5)
Benzylpenicillin	1 (0.0)	1 (0.0)	3 (0.4)	5 (0.1)
Cefazolin	75 (2.4)	32 (0.8)	-	107 (1.4)
Cefepime	139 (4.4)	103 (2.6)	103 (14.5)	345 (4.4)
Ceftazidime	13 (0.4)	18 (0.5)	-	31 (0.4)
Ceftriaxone	192 (6.1)	99 (2.5)	14 (2.0)	305 (3.9)
Cefuroxime	4 (0.1)	19 (0.5)	-	23 (0.3)
Ciprofloxacin	74 (2.3)	38 (1.0)	6 (0.8)	118 (1.5)
Clindamycin	168 (5.4)	48 (1.2)	1 (0.1)	217 (2.8)
Daptomycin	-	88 (2.2)	-	88 (1.1)
Ertapenem	-	50 (1.3)	14 (2.0)	64 (0.8)
Erythromycin	-	1 (0.0)	-	1 (0.0)
Gentamicin	7 (3.1)	28 (0.7)	12 (1.7)	137 (1.8)
Imipenem and enzyme inhibitor	3 (0.1)	11 (0.3)	-	14 (0.2)
Levofloxacin	54 (1.7)	67 (1.7)	7 (1.0)	128 (1.6)
Linezolid	78 (2.5)	30 (0.8)	21 (3.0)	129 (1.7)
Meropenem	478 (15.2)	843 (21.2)	94 (13.2)	1,415 (18.1)
Metronidazole	265 (8.5)	223 (5.6)	64 (9.0)	552 (7.1)
Nitrofurantoin	-	12 (0.3)	-	12 (0.2)
Oxacillin	86 (2.7)	53 (1.3)	-	139 (1.8)
Piperacillin and enzyme inhibitor	298 (9.5)	179 (4.5)	9 (1.3)	486 (6.2)
Polymyxin B	117 (3.7)	437 (11.0)	77 (10.8)	631 (8.1)
Sulfamethoxazole and trimethoprim	65 (2.1)	144 (3.6)	77 (10.8)	286 (3.7)
Teicoplanin	128 (4.1)	99 (2.5)	-	227 (2.9)
Tigecycline	-	83 (2.1)	3 (0.4)	86 (1.1)
Tobramycin	13 (0.4)	5 (0.1)	3 (0.4)	21 (0.3)
Vancomycin	463 (14.8)	507 (12.8)	65 (9.1)	1,035 (13.2)
Total	3.135	3.968	711	7.814

Table 4. Cost per patient according period of infection

Variable	Pre-infection period	Infection period	Post-infection period	p value*
Site of infection				
Bloodstream infection	1,218.38±1,924.47	9,577.00±16,559.45	794.18±721.77	0.05
Intra-abdominal	997.94±1,510.79	2,462.73±6,363.04	760.23±1,214.01	0.04
Urinary tract infection	859.39±1,284.94	1,444.68±2,792.39	698.26±860.52	0.04
Osteoarticular	438.03	7,193.37	-	-
Skin and soft parts	721.01±959.88	2,415.88±2,166.11	656.93±839.66	0.04
Pneumonia	1,455.96±1,818.38	2,598.74±3,391.02	1,064.52±1,653.66	0.04
Therapeutic Group				
Alimentary tract and metabolism	70.56±116.05	122.74±192.69	85.69±205.96	0.18
Anti-infective for systemic use	457.54±624.07	880.97±1,899.44	116.63±376.16	0.00
Antineoplastic and immunomodulating agents	180.83±930.93	255.15±1,007.86	3.72±13.20	0.20
Antiparasitic products, insecticides and repellents	0.57±2.90	0.26±0.91	0.20±0.87	0.86
Blood and blood forming organs	222.31±626.98	372.41±1,184.14	250.02±549.21	0.20
Cardiovascular system	35.98±71.41	37.47±49.68	26.62±61.81	0.08
Dermatological products	2.12±9.47	0.38±0.95	3.22±15.13	0.84
Genito-urinary system and sex hormones	2.66±9.23	0.72±1.85	0.20±0.53	0.22
Musculoskeletal system	10.27±29.15	28.98±122.06	12.50±46.11	0.15
Nervous system	52.16±71.21	45.30±48.16	29.58±40.11	0.11
Respiratory system	76.61±348.79	56.04±150.33	20.03±84.76	0.50
Sensory organs	6.13±32.51	6.05±28.53	5.64±9.95	0.23
Systemic hormonal preparations, excluding sex hormones and insulins	5.64±9.95	5.58±8.78	3.49±6.81	0.48
Various	3.11±10.28	7.21±21.27	7.12±20.23	0.96
General	1,169.98±1,863.07	2,017.40±3,497.01	947.77±1,369.83	0.04

Results expressed as median±standard derivation or median. * Friedman test for related samples.

❙ DISCUSSION

In this prospective cohort we found that patients infected with KPC had significantly higher costs during the period of infection, regardless the site of infection. The mean cost during hospitalization was US$ 4,135.15 per patient, of which 48.8% was during the infection, 28.3% before the infection, and 22.95% after infection. As estimated, costs improved at least 72% during the infection, as compared to other periods. These results are more significant than the impact of the prescription. Furthermore, incorrect doses or duration of treatment with antimicrobials can increase costs up to 36%.[14,15]

A significant percentage of total costs (59.5%) were due to systemic antimicrobials during hospitalization, but this figure accounts for only 7.1% of all drugs administrated. The cost of systemic antimicrobials during the infection represents 41.2% of all costs. This aspect shows the importance of antimicrobial stewardship programs considering cost-effectiveness analysis. Such programs are capable to reduce doses by 26% and expenses by 81%, representing a huge economic impact in health sector.[18] In addition, this intervention in prescription of antimicrobial therapies can reduce the spectrum of multidrug resistant bacteria.

When comparing the sites of infection, we observed significant difference only during the period of infection. The bloodstream infection presented the highest costs, followed by osteoarticular, pneumonia, intra-abdominal, skin and soft tissues, and urinary tract infection. Patients with bloodstream infection received highly doses of costly antimicrobials, such as meropenem, tigecycline and ciprofloxacin, when compared to the other sites of infection, although they did not present the highest mean treatment time. The literature shows that the treatment of bloodstream infection is more expensive, and to the use of antimicrobials to treatment of multidrug resistant bacteria can increase costs by up to 1.6 fold.[19-21] Additionally, they use more complementary drugs to fight the clinical effects of KPC infection.[22,23]

The mean time of prescription of initial antimicrobial therapy varied between 2 and 14 days. This difference in prescription days can be related to the use of second or third antimicrobial options for treating KPC infections. In most clinical cases, prolonged therapy can be beneficial; however prolonged duration of antibiotic

therapy is associated with increased resistance, drug-related effects, high costs and adverse drug reactions.[24] The use of 7 or 8 days of antibiotic therapy did not increase the risk of adverse clinical outcomes, and may reduce the emergence of resistant organisms, as compared to a prolonged course of more than 10 days.[25,26]

To our knowledge, this is the first study conducted in Latin America to measure the direct costs of KPC treatment, and it is also the first study worldwide to compare the cost of different periods of infection in this population. Most previous studies included only the cost of antimicrobials during treatment[27-29] or the general cost of hospitalization plus drug therapy.[30] Finally, our micro cost analysis allowed us to control possibly confounding influences on outcomes of cost studies, and better understand the real cost of each drug class.

While the current study enhances our understanding of the economic burden of KPC, some limitations should be considered. First, this study was conducted only in one hospital and may not be representative of all Brazil patients with KPC infection. Second, the DATASUS values may not be 100% equivalent to costs of drugs at other hospitals. Third, other cost categories, such as serum monitoring of patients, cost of materials, inputs required for preparation and administration of antibiotics, treatment of adverse reactions, and additional hospitalization time due to the presence of infectious diseases were not included in the analysis. However, there are no available cost studies with primary data collected from the Brazilian Unified Health System that could be used for comparison. Since our study did not collect data from patients without KPC, we cannot ensure that the costs were attributed exclusively to this infection.

The findings of our study indicate a thoughtful economic hazard posed by KPC that all healthcare sectors have to face. There are indirect and intangible costs that were not shown. The increasing incidence of KPC worldwide represents a growing burden that most health systems are unable to deal with. There is an imperative need to develop protocols and new antimicrobials to treat KPC, aiming to rearrange resources to increase the effectiveness of healthcare. Otherwise, the cost of treating multidrug resistant bacteria will not be feasible in a near future, with severe consequences to the population.

This study brought advances in knowledge of costs of treatment of patients with KPC infection. We verified increased costs during the period of infection in more than one drug class, and the difference in treatment cost according to the site of infection. Moreover, the direct costs were checked according to ATC classification.

❚ CONCLUSION

The direct drug cost per patient infected by *Klebsiella pneumoniae carbepemase* is conservatively estimated at nearly US$ 4,100.00, and about 60% of costs are during the period of infection. The results of this study have implications for the public health system, especially because the payment are made by the Brazilian Unified Health System. This system makes the payment according to reasons for hospitalization, however the amount reimbursed does not cover the actual value of the treatment. In addition, the treatment of some infections is not covered by this method when acquired at hospital. These data could also be used to develop appropriate cost-effectiveness models, which are needed to improve quality of treatment with reduced costs.

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