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Characterization of consumption and costs of antimicrobials in intensive care units in a Brazilian tertiary hospital

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ABSTRACT

Background: The consumption of antimicrobials and the growing resistance of infectious agents to these drugs are not related only to health issues, but also to economic parameters.

Objectives: The study objective was to evaluate the consumption of antimicrobials in General and Covid-19 Intensive Care Units (ICUs) and the impact on institutional costs in the largest institute of a tertiary public hospital.

Methods: This is a quantitative and retrospective study, which analyzed consumption, through the Defined Daily Dose (DDD), and the annual direct cost of antimicrobials in Reais (R$) and Dollars (US$), from January to December 2021.

Results: The total annual consumption (DDD/1000 patient-day) of antimicrobials in the ICUs was 14,368.85. β-Lactams had the highest total annual value, with a DDD/1000 patient-day of 7062.98, being meropenem the antimicrobial that reached the highest consumption (3107.20), followed by vancomycin (2322.6). Total consumption was higher in Covid-19 ICUs than in General ICUs, and the annual direct cost of antimicrobials in ICUs was US$560,680.79.

Conclusions: The study showed high consumption of broad-spectrum antimicrobials, highlighting the importance of structuring programs to manage the use of antimicrobials, both to reduce antimicrobial consumption and hospital costs, consolidating rational use even in pandemic scenarios.

1. Introduction

The increased consumption of antimicrobials and bacterial resistance leads to serious public health problems, as well as economic consequences due to the increased use of health resources to treat patients infected with multidrug-resistant bacteria.[1] It is estimated that by 2050, a cumulative economic output of $100 trillion is at risk. This amount includes hospital expenses, loss of labor force due to the consequences of multidrug-resistant infections, and expenses with material and health professionals. In addition to costs involving agribusiness.[2]

Of institutional hospital expenditures on medication, antimicrobials represent around 20% to 50% and consumption occurs mainly in intensive care units (ICU), with pharmacoeconomics being an important tool to promote surveillance in the use of these drugs, considering aspects of efficacy, safety, and quality.[3]

Understanding that antimicrobial resistance (AMR) has become a major public health challenge, it was necessary to draw up an action plan and measures to contain its development, such as the nationwide one aimed at preventing and controlling AMR in Brazil, effective from 2018 to 2022, which used as a basis the objectives defined by the tripartite alliance between the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE), presented in the Global Action Plan on Antimicrobial Resistance.[4]

To control antimicrobial consumption, a well-defined metric and classification system is required. With that in mind, in 1981 the WHO recommended the ATC (Anatomical Therapeutic Chemical)/DDD (Defined Daily Dose) system as an international standard for monitoring the use of medications.[5]

The Covid-19 pandemic highlighted the need for health systems to manage infectious diseases and the importance of controlling the indiscriminate use of antimicrobials. The pandemic has resulted in the excessive and misuse of antimicrobials, becoming a growing threat to human health. There is a clear relationship that excessive consumption of antimicrobials led to resistant pathogens that adversely affect human health, food security, and development.

Thus, considering the importance of controlling the consumption of antimicrobials in the hospital environment (during pandemic periods or

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not) and its impact on achieving the national action goal aimed at preventing and controlling antimicrobial resistance in Brazil, it is important to understand if the use of antimicrobial is being rational.

The objective of the present study was to evaluate the consumption of antimicrobials in General and Covid-19 specific ICUs and the impact on institutional costs in a large hospital, contributing to the understanding of the current Brazilian scenario.

2. Material and methods

This is a quantitative and retrospective study, which analyzed the consumption and direct cost of antimicrobials in intensive care units of the Central Institute of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (ICHC-FM-USP) in the period of one year (January to December 2021).

The Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (HC-FM-USP) is the largest public hospital complex in Latin America. The Central Institute is a tertiary hospital affiliated with HC-FM-USP, which has an average of 6000 health professionals, with a capacity of 1000 beds, of which 100 are in the ICU.

The first case of Covid-19 in Brazil was in the city of São Paulo - SP, in February 2020. After the WHO decreed a pandemic in March 2020, the ICHC-FM-USP became a reference in care for serious cases of the disease, where 300 ICU beds and 300 ward beds were offered for the exclusive care of patients with Covid-19. In 2021, the Central Institute had already resumed services in other specialties, but still with beds intended for this profile of patients.

2.1. Data collection

Sixteen ICUs were analyzed, 9 of which were medical specialties (General ICU) and 7 specific to patients diagnosed or suspected of having Covid-19 (Covid-19 ICU). Each ICU has approximately 13 beds.

The antimicrobials included in the study were selected according to those categorized by the Health Surveillance Coordination (COVISA) as recommended use control, as well as those previously already periodically monitored by the institution where the study took place, thus totaling 27 antimicrobials considering the oral and parenteral pharmaceutical form when necessary.

Antimicrobials were classified according to the Anatomical Therapeutic Chemical/ Anatomical classification system therapeutic Chemical - (ATC), considering the 5 hierarchical levels.

2.1.1. Consumption of antimicrobials

The metric used to estimate antimicrobial consumption was the Defined Daily Dose (DDD) per 1000 patient days. Data were extracted from the institutional report generated periodically in the form of an Excel spreadsheet for the Hospital Infection Control Commission (CCIH) of the hospital, which has the following antimicrobial information: generic name, presentation, number of units consumed (measured from the quantity of item supplied by the pharmacy), the value of consumption in grams, number of area codes and the total number of patient-days. This information is available in the form of monthly and annual reports. However, for the present study, the total annual DDD value of each antimicrobial will be considered.

The DDD calculation is carried out following the guidelines of the Ministry of Health and the World Health Organization, according to the formula:

$$\text{DDD}/1000 \text{ patient days} = \frac{A/B}{P}$$

Where: A = Total antimicrobial consumed in grams (g), in the month of surveillance. B = Standard daily dose of antimicrobial calculated in grams for an adult weighing 70 kg, without Renal Failure. P = Patient days, in the month of surveillance.

2.1.2. Direct cost

The number of units consumed (measured based on the quantity of the item served by the pharmacy) was extracted from the institutional DDD report and the monetary value of each antimicrobial was extracted from the Dynamics AX GRP program, which details the price record of the institutional purchase of medicines in the Brazilian currency Real (R$).

Thus, the annual institutional direct cost of each antimicrobial in the ICUs was estimated by multiplying the number of units consumed by the unit value of each antimicrobial.

It should be noted that indirect costs related to the use of antimicrobials, such as hospitalization, procedures, and laboratory investigation, were not calculated, since this is a study carried out from the perspective of the pharmacy sector.

2.1.3. Data analysis

Data were extracted from institutional reports and spreadsheets, exported to a computerized spreadsheet, and analyzed based on DDD/1000 patients day in General ICU *versus* Covid-19 ICU.

3. Results

The total consumption (DDD/1000 patient day) of antimicrobials in 2021 was 14,368.85. β-Lactams had the highest annual total value (49.15%), with a DDD/1000 patient day of 7062.98, with meropenem being the antimicrobial that achieved the highest consumption (3104.20). The second family of antimicrobials with the highest consumption of DDD/1000 patient days were glycopeptides (2408.83; 16.76%) followed by antimycotics (1991.95; 13.86%), polymyxins (1236.33; 8.60%), fluoroquinolones (1185.23; 8.24%), other antimicrobials (365.42; 2.54%) and tetracyclines (118.11; 0.82%) (Table 1).

When stratified by ICU profile, differences in the value of DDD/1000 patient-days were observed. Both in the General ICU and in Covid-19, the antimicrobials in the first and second positions of consumption were meropenem and vancomycin. However, the third most consumed in the General ICU was ceftriaxone, followed by piperacillin-tazobactam and fluconazole. While, in the Covid-19 ICU, this order was different, with piperacillin-tazobactam being the third most consumed, followed by fluconazole and ceftriaxone, when individually comparing the consumption of each of these five antimicrobials in the two ICU profiles under analysis. Furthermore, we can observe that the DDD/1000 total patient days in the year 2021 was 17.74% higher in the Covid-19 ICU (8459.23) when compared to the General ICU (5909.62), although the total number of patient-days was lower in the Covid-19 ICU (15,202.00) than in the General ICU (31,044.00), signaling a higher consumption of antimicrobials in this ICU profile (Fig. 1).

The annual institutional cost of antimicrobials in ICUs in 2021 was R$ 3,027,676.30 (US$ 560,680.79). The cost was 31.88% higher in the General ICU (R$ 1,996,537.27; US$ 369,729.12) than in the Covid-19 ICU (R $ 1,031,139.03; US$ 190,951.67). The antimicrobial that accounted for about 1/3 of the expenses was from the class of antimycotics, liposomal amphotericin B (R$ 1,090,400.00; US$ 201,925.92), although it was not the antimicrobial with the highest consumption in the period under study, occupying the 15th place with an annual DDD/1000 patient day of 109.62 (Table 2).

4. Discussion

The WHO developed the DDD as a unit of drug use, which is defined as the average daily dose of a drug for its main indication in adults.[6] In the present study, it was possible to observe a high consumption of broad-spectrum antimicrobials, mainly meropenem, and vancomycin, in 1 year, in the largest institute of a tertiary public hospital. This consumption profile is observed in Latin America, probably due to the prevalence of infections caused by gram-negative bacteria that produce extended-spectrum β-lactamase (ESBL) and methicillin-resistant *Staphylococcus aureus* (MRSA), respectively.[7] The high consumption of broad-spectrum

Table 1
Consumption of antimicrobials in grams and in DDD per 1000 patient-days in 2021.

Antimicrobial	ATC	General ICU		Covid-19 ICU		Total	
		Consumption (g)	DDD/1000 patient-days	Consumption (g)	DDD/1000 patient-days	Consumption (g)	DD/1000 patient-days
ß-Lactams	–	52,626.5	2957.05	39,038.5	4105.93	91,665.0	7062.98
Meropenem 1 g e 0.5 g inj.	J01DH02	11,202.0	1137.68	9230.0	1966.52	20,432.0	3104.20
Piperacillin-tazobactam 4.5 g inj.	J01CR05	31,192.0	655.79	25,212.0	1138.59	56,404.0	1794.38
Ceftriaxone (sodium) 1 g inj.	J01DD04	6772.0	933.84	2859.0	759.24	9631.0	1693.08
Ceftazidime 1 g inj.	J01DD02	1781.0	144.90	655.0	100.75	2436.0	245.65
Ceftazidime-avibactam 2.5 g inj.	J01DD52	760.0	30.99	682.50	63.79	1442.50	94.78
Cefepime 1 g inj.	J01DE01	291.0	21.48	242.0	49.18	533.0	70.66
Cefotaxime 1 g inj.	J01DD01	614.0	30.91	–	–	614.0	30.91
Imipenem 0.5 g inj.	J01DH51	14.50	1.46	29.0	22.04	43.50	23.50
Ampicillin-sulbactam 3 g inj.	J01CR01	–	–	129.0	5.82	129.0	5.82
Glycopeptides	–	6645.9	1013.21	4695.8	1395.62	11,341.7	2408.83
Vancomycin 0.5 g inj.	J01XA01	6596.50	979.83	4648.0	1342.83	11,244.50	2322.66
Teicoplanin 0.2 g e 0.4 g inj.	J01XA02	49.40	33.38	47.80	52.79	97.20	86.17
Antimycotics	–	461.10	703.76	371.95	1288.19	833.05	1991.95
Fluconazole 0.2 g inj.	J02AC01	364.20	512.25	319.20	1026.15	683.40	1538.40
Anidulafungin 0.1 g inj.	J02AX06	40.10	115.14	24.40	170.94	64.50	286.08
Liposomal amphotericin B 0.05 g inj.	J02AA01	45.40	57.34	12.60	52.28	58.0	109.62
Voriconazole 0.2 g inj.	J02AC03	7.80	2.98	15.20	34.65	23.0	37.63
Amphotericin B deoxycholate 0.05 g inj.	J02AA01	1.50	11.34	0.25	3.39	1.75	14.73
Micafungin 0.1 g inj.	J02AX05	2.10	4.71	0.30	0.78	2.40	5.49
Polymyxins	–	311.58	427.93	300.24	808.40	611.82	1236.33
Polymyxin E 0.033 g e 0.15 g inj.	J01XB01	209.65	232.02	174.43	410.71	384.08	642.73
Polymyxin B 0.05 g inj.	J01XB02	101.93	195.91	125.81	397.69	227.74	593.60
Fluoroquinolones	–	1218.3	524.32	646.55	660.91	1864.85	1185.23
Levofloxacin 0.5 g inj.	J01MA12	284.50	189.24	303.0	358.44	587.50	547.68
Ciprofloxacin 0.2 g inj.	J01MA02	721.80	256.17	245.80	194.38	967.60	450.55
Ciprofloxacin 0.5 g tab.	J01MA02	148.50	41.79	71.25	72.59	219.75	114.38
Levofloxacin 0.5 g tab.	J01MA12	63.50	37.12	26.50	35.50	90.0	72.62
Other antimicrobials	–	544.4	201.79	211.50	163.63	755.9	365.42
Linezolid 0.6 g inj.	J01XX08	395.80	93.33	195.20	119.36	591.0	212.69
Daptomycin 0.5 g inj.	J01XX09	99.50	96.81	14.50	42.78	114.0	139.59
Linezolid 0.6 g tab.	J01XX08	49.10	11.65	1.80	1.49	50.90	13.14
Tetracyclines	–	25.60	81.56	12.80	36.55	38.40	118.11
Tigecycline 0.05 g inj.	J01AA12	25.60	81.56	12.80	36.55	38.40	118.11
Total		61,833.38	5909.62	45,277.34	8459.23	107,110.72	14,368.85

ATC, Anatomical Therapeutic Chemical; DDD, Defined Daily Dose; inj., injectable; tab., tablet.

antimicrobials was also observed in studies that analyzed the pattern of antibacterial in intensive care units, showing a high consumption of β-Lactams, mainly ceftriaxone, which was also among the most consumed antimicrobials in our study.[8,9]

The excessive and unnecessary use of antibiotics implies antimicrobial resistance, caused by the emergence of multidrug-resistant organisms, representing a new threat to public health by increasing morbidity, mortality, and health costs.[10] In times of overload and urgency, such as the pandemic, it is common for health systems to act in non-compliance with the best practices for controlling nosocomial infections. Regarding antimicrobial prescription practices, studies have shown that during Covid-19 there were fluctuations in consumption, with the first wave being responsible for the high consumption of azithromycin, and doxycycline.[11] At the same time, Khamis et al.[12] verified a high consumption of ceftriaxone, amoxicillin and piperacillin/tazobactam.

Given the uncertainty of the infectious diagnosis combined with the high severity of the patient with Covid-19, studies have shown that most patients were being unnecessarily treated with antibiotics, allowing the increase in bacterial resistance, which may show long-term consequences.[13,14] A meta-analysis performed with 30,000 patients revealed that the prevalence of bacterial infections in patients with Covid-19 was 8.6% and 64% of them had at least a prescribed antibiotic.[15]

The high consumption of antibiotics during a viral pandemic is probably because results based on the influenza pandemic in 2009 showed that rates of co-infections were determinant for worse prognoses/outcomes.[16] This consumption decreased with the introduction of guidelines guiding disease management.[17] The analysis of the data from this study showed that the most consumed antibiotics during the year 2021 were: meropenem, vancomycin, and piperacillin-tazobactam, in the total number of ICUs. A study in Scottish hospitals found that in critical patients the prescription of meropenem and piperacillin-tazobactam were more frequent and of late use, suggesting suspected nosocomial infection, even though there was no collection of microbiological data.[18]

A possible explanation for the high incidence of nosocomial infections, justifying the use of broad-spectrum antibiotics, is the fact that patients with Covid-19 admitted to the ICU require prolonged respiratory support, ventilation in the prone position, and support for other vital organs, creating a highly favorable environment for healthcare-associated infections and highly challenging for healthcare staff.[19]

When comparing the institute's data with those released by the Municipal Center for Hospital Infection Control (NMCIH) of the Epidemiological Surveillance Division of COVISA in the state of São Paulo, in the first half of 2021 (January to June), ceftriaxone was the most common antimicrobial consumed in public hospitals in both ICUs. However, in the present study, ceftriaxone appeared as the 5th most consumed in the Covid-19 ICU and 3rd in the General ICU. This difference may be related to the understanding of the low association of community infections in patients with Covid-19, thus decreasing the consumption of ceftriaxone at the institute.[20]

Analyzing antimycotics in ICUs, this group also showed a high consumption, mainly fluconazole, with a DDD/1000 patient-day of 1538.40,

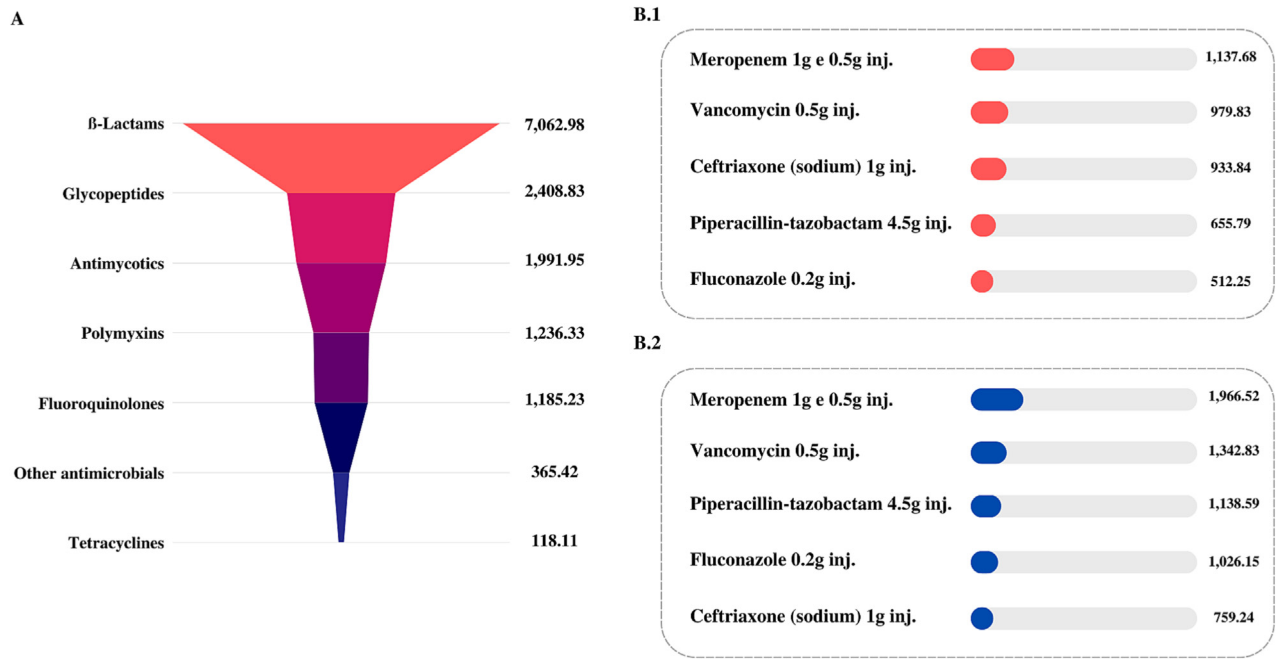

Fig. 1. Total consumption of antimicrobials per family evaluated by DDD/1000 patient-days in all ICUs (A); per drug in the General ICU (B·I) and in the Covid-19 ICU (B.2) in the period of 2021. inj., injectable.

being the 5th most consumed antimicrobial in the General ICU (515.25) and the 4th most consumed in the Covid-19 ICU (1026.15). Higher consumption in the Covid-19 ICU may be related to findings already described in the literature that severe fungal infections are not uncommon in patients with Covid-19.[21,22] However, further analyzes are needed to better understand this consumption profile.

When we think about hospital costs, it is always a great challenge to manage the available budget and provide the most cost-effective health technology. Antimicrobials represent a large part of these expenses and several studies have already shown a high prescription rate for patients admitted to ICUs. In a tertiary hospital in Pakistan, it was found that empirical use of antimicrobials was initiated in 68% of patients, while sensitivity testing of culture was performed in only 19% of patients.[23] In Brazil, in a multicenter study that analyzed 35 ICUs, a prevalence of antimicrobial use of 52.4% was observed, with empirical use being more predominant (62.6%).[22]

Thus, the high use of antimicrobials in ICUs increases hospital costs with medication, as it was possible to observe in our ICUs an estimated annual expenditure of R$ 3,027,676.30 (US$ 560,680.79). In a retrospective analysis carried out in the ICU of a university hospital in Morocco, annual expenditure on antimicrobials of US$ 118,224.00 was verified, but considering a significantly lower total patient-day than that of the present study.[8] And in a tertiary hospital in China, with a higher number of patient days, an annual cost of US$ 4,640,000.00 was verified.[9]

With this, it is understood the importance of the management and control of the stock of medicines in the hospital environment, being possible to observe in the present study, that only one item can compromise a great part of the institutional costs. A tool used in hospitals is the ABC Curve, which allows the classification of drugs statistically, according to the financial impact and demand for use, with classification A being that item that, despite low consumption, has a high financial value.[25] Therefore, it is a tool that assists in inventory management and better use of financial resources.[26]

Given this scenario, where the need for rational use of antimicrobials is increasingly evident, both for the reduction of ADRs and for the reduction of hospital costs, antimicrobial stewardship has proven to be an important tool in the hospital environment. It is a program that aims to help antibiotic therapy and promote quality patient care through the appropriate selection, dose, route of administration, and duration of treatment.[27] Studies have already reported a decrease in ADRs after implementing antimicrobial stewardship, with a reduction in the use of antimicrobials and, consequently, in costs.[28,29] However, the use of this antimicrobial use management program still needs to be strengthened within hospital environments, and it is possible to observe that even in environments that already had antimicrobial stewardship, there was an inappropriate consumption of antimicrobials during Covid-19.[30]

Although the WHO has already decreed the end of the global emergency, it is necessary to review everything that was done during the Covid-19 pandemic and identify mistakes and successes to prepare for the next ones. And the study of the use of antimicrobials and the need to align with stewardship programs can prevent a bacterial pandemic, which was as bad, or worse than that of Covid-19.

The retrospective analysis of the use of antimicrobials in patients with Covid-19 compared to patients in the general ICU provides an insight into how we are using these drugs. These results will serve as a basis for boosting the stewardship program at the institution, and its application in other public hospitals in the country. With the aim of promoting rational use, avoiding unnecessary costs to the health system, and serving as literature for future health emergencies, such as the pandemic.

Our study has some limitations, such as being carried out in a single center, analyzing only 27 antimicrobials, and considering only direct costs related to the drug. It is also difficult to compare the results obtained with other data available in the literature, mainly due to the size and complexity of the hospital where the present study was carried out. Despite the limitations, the results found here will contribute to the understanding of antimicrobial consumption and its impact on hospital costs, promoting continuing education for health professionals and consolidating a rational use of antimicrobials.

5. Conclusion

Antimicrobial consumption (DDD/1000 patient day) was higher in ICUs Covid-19 than in the General ICUs in one year, with the broad spectrum agents being the most consumed in both ICUs (meropenem and vancomycin). The estimated annual expenditure on antimicrobials was US$ 560,680.79. The need to structure programs to manage the use of

Table 2
Direct cost of antimicrobials in Reais (R$) and Dollar (US$) in 2021.

Antimicrobial	General ICU	Covid-19 ICU	Total	
	Cost (R$)	Cost (R$)	Cost (R$)	Cost (US$)
Antimycotics	953,482.0	307,415.0	1,260,897.0	233,499.44
Liposomal amphotericin B 0.05 g inj.	853,520.0	236,880.0	1,090,400.0	201,925.92
Anidulafungin 0.1 g inj.	67,744.94	41,221.36	108,966.3	20,178.94
Fluconazole 0.2 g inj.	20,941.5	18,561.0	39,502.5	7315.27
Voriconazole 0.2 g inj.	5054.4	9849.6	14,904.0	2760.0
Micafungin 0.1 g inj.	5599.44	799.92	6399.36	1185.06
Amphotericin B deoxycholate 0.05 g inj.	621.6	103.6	725.2	134.29
ß-Lactams	644,850.34	479,710.80	1,124,561.14	208,252.06
Ceftazidime-avibactam 2.5 g inj.	183,616.0	164,892.0	348,508.0	64,538.51
Piperacillin-tazobactam 4.5 g inj.	110,575.64	91,319.2	201,894.84	37,387.93
Meropenem 1 g e 0.5 g inj.	244,673.1	183,424.5	428,097.60	79,277.33
Cefepime 1 g inj.	5814.18	4915.08	10,729.26	1986.9
Ceftazidime 1 g inj.	60,554.0	22,270.0	82,824.0	15,337.77
Ceftriaxone (sodium) 1 g inj.	29,187.32	12,374.01	41,561.33	7696.54
Cefotaxime 1 g inj.	9824.0	–	9824.0	1819.25
Imipenem 0.5 g inj.	606.1	–	606.1	112.24
Ampicillin-sulbactam 3 g inj.	–	516.0	516.0	95.55
Polymyxins	95,542.72	99,944.26	195,486.98	36,201.29
Polymyxin E 0.033 g e 0.15 g inj.	64,195.44	54,315.46	118,510.90	21,946.46
Polymyxin B 0.05 g inj.	42,387.28	52,748.8	95,136.08	17,617.79
Tetracyclines	99,840.0	49,920.0	149,760.0	27,733.33
Tigecycline 0.05 g inj.	99,840.0	49,920.0	149,760.0	27,733.33
Fluoroquinolones	71,995.60	31,105.25	103,100.85	19,092.75
Ciprofloxacin 0.2 g inj.	63,157.5	21,507.5	84,665.0	15,678.70
Ciprofloxacin 0.5 g tab.	53.13	21.21	74.35	13.76
Levofloxacin 0.5 g inj.	8722.77	9550.59	18,273.36	3383.95
Levofloxacin 0.5 g tab.	62.20	25.95	88.16	16.32
Glycopeptides	56,607.02	36,832.18	93,439.2	17,303.55
Vancomycin 0.5 g inj.	51,625.6	32,119.8	83,745.4	15,508.40
Teicoplanin 0.2 g e 0.4 g inj.	4981.42	4712.38	9693.80	1795.14
Other antimicrobials	63,180.0	19,091.0	82,271.0	15,235.37
Linezolid 0.6 g inj.	29,084.0	14,564.0	43,648.0	8082.96
Linezolid 0.6 g tab.	4046.7	148.05	4194.75	776.80
Daptomycin 0.5 g inj.	30,049.0	4379.0	34,428.0	6375.55
Total	1,996,537.27	1,031,139.03	3,027,676.30	560,680.79

inj., injetável; tab., tablet.

antimicrobials is highlighted, both to reduce consumption and also hospital costs, consolidating rational use even in pandemic scenarios.

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Author contributions

Tázia Lopes de Castro: conceived/planned the original idea, collected/analyzed data, wrote the article. Amanda Magalhães Vilas Boas Cambiais: critical review of the article. Andrea Cássia Pereira Sforsin: critical review of the article. Vanusa Barbosa Pinto: critical review of the article. Maria Alice Pimentel Falcão: data analysis, and article writing. All authors read and approved the final manuscript.

Declaration of Competing Interest

None.

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