ORIGINAL ARTICLE

Use of Antimicrobials in a Specialized Cardiology Hospital

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Highlights
1. Despite a lower percentage of inadequacies, they were maintained for several days.
2. Necessary enhancing traceability of information associated with treatments.
3. It is crucial to strengthen the adequate use of clinical laboratories and its results.

ABSTRACT

The management of antimicrobial use has been recognized as a relevant action to mitigate irrational use and the increasing resistance to this class of drugs. Thus, the present study aimed to evaluate the use of antimicrobials by measuring consumption and assessing the appropriateness of treatment regarding indication, dose, and duration, from August to November 2019, in a cardiology specialized hospital. Empirically initiated treatments were also evaluated for their adequacy following culture results and antimicrobial sensitivity testing, with adjustments made as necessary. Additionally, the World Health Organization (WHO) classification was applied, categorizing antimicrobials into Access, Watch, and Reserve (AWaRe) groups based on the impact of their use on microbial resistance and the importance of their appropriate and restricted use. A total of 1558 prescriptions associated with 405 treatments were evaluated. The most commonly used therapeutic classes were combined penicillins, carbapenems, and third-generation cephalosporins. Adequacy in indication was observed in 84.2% of cases. Among these, 88.1% and 90.6% exhibited appropriate dose and treatment duration, respectively. Empirically initiated treatments were predominantly conducted (58.7%) with antimicrobials from the Watch group, followed by the Reserve group (23.5%) and Access group (17.8%). Therapy adjustment was performed in 59% of cases requiring it (57.9%). The results suggest that antimicrobial use should be optimized, aiming to minimize empirical use, favor the use of antimicrobials from the Access category, and promote the adequacy of empirical treatments following culture results.

Keywords: drug utilization review; antimicrobial stewardship; drug resistance multiple bacterial.

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INTRODUCTION

Antimicrobial resistance and the increasing detection of multi-resistant microorganisms represent a global public health concern. Irrational use, whether associated with prescribing antimicrobials for inappropriate indications and/or incorrect doses and/or treatment durations, is of the factors linked to this phenomenon. The inappropriate use of antimicrobials also leads to therapeutic ineffectiveness, increased morbidity, mortality, length of hospital stays, adverse events, and associated treatment costs[1,2].

A study conducted in the United States[3] in 2017 identified that 16% of the administered doses, totaling 145 days of treatment, were unnecessary. Additionally, 43% of empiric treatments were inadequate; 77% of opportunities for therapy adjustment following microbiological culture results were missed, and 48% should have been discontinued due to incorrect diagnosis but were not. In total, the estimated extra cost due to inappropriate antimicrobial use amounted to $23,524.00.

An evaluation of antimicrobial use at a trauma center in a tertiary hospital in India[4], conducted prior to the implementation of an Antimicrobial Stewardship Program (ASP), identified inadequacy in antimicrobial selection for clinical indications in 17.2% of treatments, 10.9% for route of administration, and 18.7% for inappropriate duration.

The ASP has been implemented as a strategy for better control of antimicrobial use. Studies conducted in various countries have observed positive outcomes, including reduced antimicrobial consumption, improved treatment adequacy regarding indication, dose, and duration, decreased use of broad-spectrum antimicrobials, and consequently, reductions in costs and the selection of antimicrobial-resistant strains[3–7].

In Brazil, the Brazilian Health Regulatory Agency (Anvisa) released a national guideline for the development of ASPs in 2017[1]. The Stewardship Brazil project, conducted in 2019 to evaluate the implementation of ASP in hospitals with intensive care units across the country, achieved voluntary participation from 55% of establishments. Among these, 47.5% of hospitals had the program in operation[8].

In 2021, the World Health Organization (WHO) released the AwaRe classification of antimicrobials into three categories based on the impact of inappropriate antimicrobial use on microbial resistance and the level of restriction and monitoring of their use[9].

The Access category encompasses antimicrobials for which pathogens typically exhibit a sensitivity profile and have a reduced potential for promoting resistance. They should be the first and second choice for empirical treatment. The Watch group consists of antimicrobials with a higher potential for selecting resistant microorganisms and should be used empirically in specific situations. In contrast, the Reserve category antimicrobials should be the last resort for infection suspected cases by multidrug-resistant microorganisms, in scenarios where therapeutic alternatives have not been successful, or in confirmed cases[9].

In this context, the present study aims to analyze the use of antimicrobials in a high-complexity public institution specialized in cardiology, where there is no ASP or specific pharmacist involvement, to identify the pattern of antimicrobial utilization. Thus, the study intends to support the establishment of needs and priorities to be addressed when implementing an ASP or even identifying measures that can be adopted, regardless of establishing the program, aiming for the rational use of these medications.

METHOD

A descriptive retrospective study with quantitative analysis was conducted based on prescriptions of systemic antimicrobials in a specialized cardiology hospital with 165 beds.

The project was approved by the Research Ethics Committee of the institutions involved, with protocol numbers CAAE 33565120.8.0000.5626 and 33565120.8.3001.5272, respectively.

The study included prescriptions from two intensive care units, one semi-intensive unit, and four general wards, involving participants over 18 years old who were hospitalized from August 1, 2019, to November 30, 2019, and received treatment with at least one systemic antimicrobial. Prescriptions from patients discharged within 24 hours of admission, treatments involving antifungals and antivirals and treatments initiated before the study period or completed after the study period were excluded from the analysis.

After the selection of prescriptions included in the study, the treatments were analyzed by reviewing of the patient's medical records and laboratory test results throughout the entire treatment period.

Analysis of consumption data

The medication consumption data were evaluated using the indicators recommended by the National Guideline for the Development of Antimicrobial Stewardship Programs in Healthcare Facilities by the WHO[1]. The first indicator used was Defined Daily Dose (DDD), the second was Duration of Therapy (DOT), and the third was Length of Therapy (LOT), all expressed per 100 bed days and following the Anatomical Therapeutic Chemical Classification (ATC).

Determination of antimicrobial utilization profile

Initially, the age and sex of the participants were identified, along with the prescribed antimicrobials and whether the treatment was conducted as monotherapy or polytherapy. Prescriptions and antimicrobial treatments were evaluated for indication, dose, and duration based on institutional guidelines and in their absence through the UpToDate® database. The presence or absence of institutional guidelines was another variable considered.

The treatments were classified as prophylactic, empirical, and guided. In the case of empirical treatments, it was also verified whether microbiological culture was requested, the timing of collection (before or after the start of therapy), and the adjustment of therapy following microbiological culture results and antimicrobial sensitivity testing.

The analysis of dose and duration was only performed for treatments with therapeutic indications deemed appropriate. For the dose adequacy analysis, antimicrobials prescribed with the correct proposed dose were identified, both with and without the need for adjustment, and in cases requiring adjustment, whether it was done correctly. The duration analysis was conducted considering both the proposed and the actual durations based on the maximum recommended time in the databases used as reference.

The analysis of dose, duration, and, in the case of empirically initiated treatments, therapy adjustment following microbiological culture results were performed by evaluating all prescriptions for each treatment.

The WHO's AWaRe classification was employed for characterizing antimicrobials used empirically[9].

RESULTS

During the study period, 10,849 prescriptions were analyzed, with 1,975 (18.2%) including systemic antimicrobials. A total of 417 prescriptions were excluded: 127 due to treatments starting before or finishing after the study period. A total of 1,558 (14.4%) prescriptions were evaluated, associated with 161 (4.4%) patients and 405 treatments. The patients had a mean age of 54.9 years, ranging from 18 to 90 years, and were predominantly male (86 - 53.4%).

The treatments were predominantly monotherapy (185 - 64.7%). Treatments involving two antimicrobials accounted for 18.2% (52), those with three antimicrobials 8% (23), and those with more than four antimicrobials 9.1% (26).

Analysis of Consumption Data

The calculation of antimicrobial consumption in DDD per 100 bed days revealed notable figures for specific drug classes, including combined penicillins (7.43), carbapenems (7.22), third-generation cephalosporins (5.02), daptomycin (4.6), glycopeptides (3.86), broad-spectrum penicillin (2.93), and polymyxins (2.67). The individual analysis of antimicrobial consumption is presented in Table 1.

Table 1 – Antimicrobials with the highest consumption during the study period. Rio de Janeiro, 2019

Antimicrobial	DDD WHO 2021 (g)	DDD/100 bed days
Meropenem	3	7,00
Piperacillin-tazobactam (based on piperacillin)	14	5,06
Ceftriaxone	2	4,78
Daptomycin	0,28	4,60
Vancomycin	2	3,86
Polymyxin B Sulfate	0,15	2,67
Amoxicillin	1,5	1,56
Linezolid parenteral administration	1,2	1,55
Ampicillin	6	1,37
Tigecycline	0,1	1,23
Doxycycline	0,1	1,13
Amikacin	1	1,08
Oxacillin	2	1,00
Amoxicillin + clavulanate parenteral administration	3	0,81
Oral Cefuroxime	0,5	0,68

In the intensive care units, the assessment of antimicrobial usage periods identified 53.68 DOT per 100 bed days and 27.16 LOT per 100 bed days. In the wards, 32.49 DOT per 100 bed days and 23.57 LOT per 100 bed days were observed. Regardless of the unit, the analysis of all treatments identified 40.29 DDD per 100 bed days and 24.89 LOT per 100 bed days.

Determination of Antimicrobial Utilization Profile

The analysis regarding the clinical adequacy of prescribed antimicrobials was predominantly conducted (251 – 62.0%) using the UpToDate® database, followed by the institutional protocol (100 – 24.7%). In 7.9% (32) of cases, the analysis was conducted using institutional protocols and UpToDate®. In 5.4% (22) of cases, the indication evaluation was not possible due to the lack of treatment justification in the prescription. The adequacy of indication, regardless of the type of treatment, was identified in 84.2% (341) of cases.

The empirical use of antimicrobials was more frequent, representing 215 treatments (53.1%), followed by prophylactic use (100 – 24.7%), guided use (55 – 13.6%), those without justification field completion (22 – 45.4%), and for pre-existing patient conditions (13 – 3.2%).

Table 2 summarizes the analyses of indication, dose, intended duration, and total presented below for each type of treatment.

Table 2 – Antimicrobial utilization profile after the analysis of treatments regarding indication, dose, and duration. N= 370, Rio de Janeiro, 2019

Treatment					
Treatment Type	Empirical		Guided		Prophylactic
	n	%	n	%	n	%
Therapeutic indication						
Appropriate indication	194	90.2	52	94.5	95.0	95.0
Without indication	21	9.8	3	5.5	5.0	5.0
Dose*						
Appropriate dose	128	66.0	31	59.6	94	98.9
Higher dose	4	2.1	3	5.8	0	0.0
Lower dose	5	2.6	0	0.0	1	1.1
Dose adjustment properly performed	33	17.0	13	25.0	0	0.0
Dose adjustment inadequately performed	3	1.5	4	7.7	0	0.0
No dose adjustment performed when renal function required	21	10.8	1	1.9	0	0.0
Treatment duration intended*						
Appropriate	178	91.8	49	94.2	82	86.3
Longer	6	3.1	1	1.9	12	12.6
Shorter	8	4.1	2	3.8	1	1.1
Not Specified	2	1.0	0	0.0	0	0.0
Treatment duration implemented**						
Appropriate	92	60.5	33	89.2	82	86.3
Longer	9	5.9	0	0.0	12	12.6
Shorter	51	33.6	4	10.8	1	1.1

* Evaluation conducted in treatments with appropriate therapeutic indication (empirical n=194; guided n=52; prophylactic n=95);

** Evaluation conducted in treatments where discontinuation was not associated with patient discharge/death or switch to another medication (empirical n=152; guided n=37; prophylactic n=95).

Prophylactic Treatments

Prophylactic treatments initiated were in accordance with a clinical indication in 95% (95) of cases, with the majority (87 - 87%) following institutional protocols.

Of the 95 antimicrobials prescribed for prophylaxis, 98.9% (94) had the appropriate dosage, and 86.3% (82) had the intended duration. All treatments with an intended duration longer than recommended (12 – 12.6%) were associated with prophylaxis for infective endocarditis (IE) in dental procedures. The evaluation of total duration identified that 82 (86.3%) had adequate duration. Four treatments initially had inadequate duration and were subsequently adjusted. In total, 12 (12.6%) treatments had a duration longer than recommended and were indicated for prophylaxis for IE during dental procedures.

Guided Treatments

Out of the 55 guided treatments, three (5.4%) were guided by detecting antibodies to *Treponema pallidum*. Six (10.8%) did not have the sensitivity test result in the electronic system, and 14 (25.2%) did not have the antimicrobial prescribed, nor did a representative of its class tested for sensitivity.

In 26 (47.3%) treatments, an antimicrobial to which the identified microorganism was sensitive was prescribed. In two cases (3.6%), Meropenem and Amikacin were prescribed, antimicrobials to which the identified microorganism, Carbapenemase-producing *Klebsiella pneumoniae*, was resistant.

In four cases, the blood culture result was negative. In one of them, the patient presented clinical patterns with altered inflammatory markers indicative of sepsis. In the other three cases, a clinical indication of IE with vegetation was identified by computed tomography. Therefore, the treatments were maintained even with negative cultures.

In the case of guided treatments, 44 (84.6%) out of 52 antimicrobials analyzed had adequate doses. Among these, 29.5% (13) required adjustment due to renal function. Dose errors detected in guided treatments were related to incorrectly performed dose adjustments (4 – 7.7%), doses higher than recommended (3 - 5.8%), and absence of adjustment (1 – 1.9%).

The adequacy of the proposed duration in the prescription was verified in 49 (94.2%) of the guided treatments with appropriate indications. Another 3.8% (2) had a shorter duration, and 1.9% (1) had a longer duration. The evaluation of the total duration of treatment (n=37), excluding treatment interruptions due to patient death or discharge and medication changes, identified adequacy in 89.2% (33) of the treatments.

Empirical Treatments

Most empirical treatments (194 - 90.2%) had appropriate indications. The most frequent indications were sepsis (66 – 30.7%), pneumonia (37 – 18.1%), IE (16 – 7.4%), post-operative wound infections (15 – 7.0%), and urinary tract infections (14 – 6.5%).

Laboratory tests for identifying the microorganism associated with the patient's clinical condition were requested in 79.5% (171) treatments. Only 44.4% (77) of the reports were made available before the end of treatment. In 52 (68.4%) of these reports, at least one microorganism was identified, and in 25 (31.6%), no microorganism was identified.

Among the 52 antimicrobials prescribed with positive microbiological results, 16 (30.8%) were appropriate, 18 (90%) were incorrect and were adjusted, and two (10%) were incorrect and were not adjusted. In 16 (9.4%) cases, however, the antibiogram result was not available in the electronic system, or the prescribed antimicrobial or representative of the class had not been tested, making it impossible to assess the adequacy of treatment. Among the prescribed antimicrobials associated with negative microbiological laboratory results, 16 (66.7%) were maintained, and 8 (33.3%) were discontinued. Therefore, out of the 44 (57.9%) treatments that should have been discontinued or adjusted, only 26 (59%) were reviewed.

The adequacy evaluation of prescribed doses in treatments with clinical indication (194) identified that 83.0% (161) were prescribed at the appropriate dose, among which 20.5% (33) required adjustment for renal function. Among the 33 (17.0%) antimicrobials prescribed with inadequate doses, the main reasons were non-compliance with the need for renal function adjustment (21 – 63.6%), followed by prescription of a dose lower than recommended (5 – 15.2%), overdose (4 – 12.1%), and incorrect adjustment of dose for renal function (3 – 9.1%).

The assessment of the intended duration of treatments identified adequacy in 178 (91.8%); 4.1% had a shorter duration, and 3.1% had a longer duration. Among these treatments, an error in registering Cefepime 2g in the hospital system was identified, which prevented the insertion of the desired treatment period. This situation was observed in 2 treatments (1.0%).

The total duration performed was evaluated in 152 treatments, excluding interruptions of treatment due to patient discharge/death and medication changes, and identified adequacy in 92 (60.5%) of the treatments and shorter duration in 51 (33.6%) cases.

Empirically initiated treatments were predominantly conducted (125 – 58.7%) with antimicrobials from the Watch group, followed by the Reserve group (50 – 23.5%) and the Access group (38 – 17.8%). Antimicrobials from the Watch and Reserve categories were more frequently prescribed in intensive care units, accounting for 72% (90) and 80% (40). The Access category was more commonly prescribed in the wards (23 – 60.5%) (Figure 1).
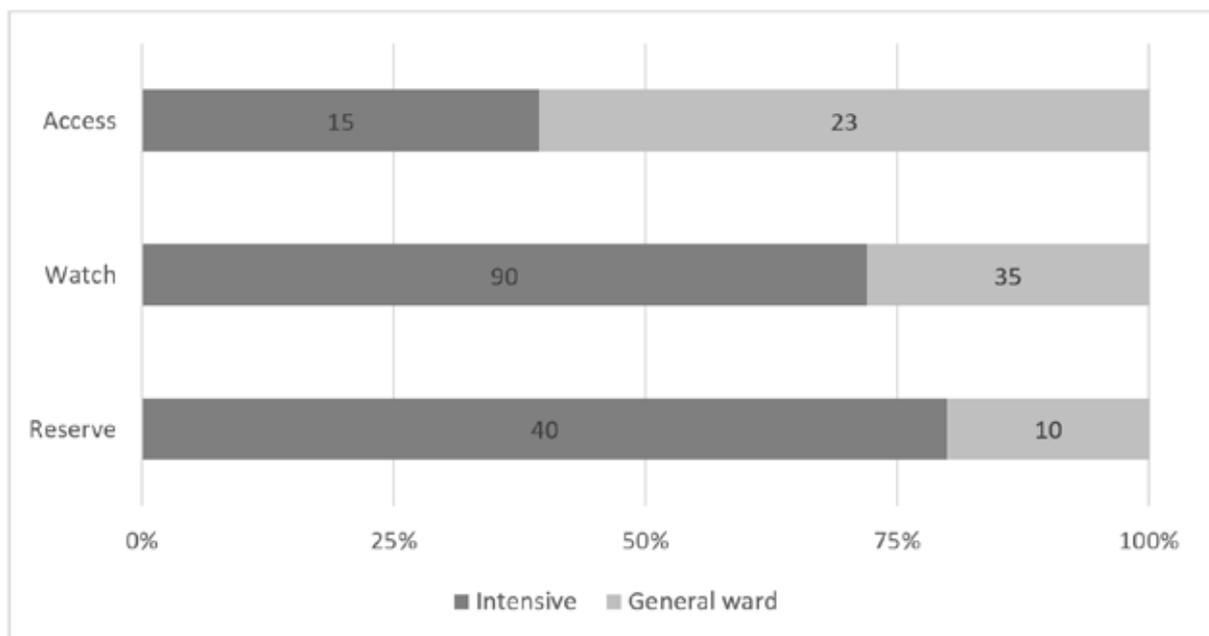

Figure 1 – Distribution of empirically used antimicrobials according to the WHO's AWaRe classification (WHO 2021) and the type of unit of use, N=215, Rio de Janeiro, 2019.

DISCUSSION

In 2017, a prevalence study on antimicrobial usage was conducted following the international methodology of the Global Point Prevalence Survey (Global-PPS) in 18 Brazilian hospitals[10]. The patient profile identified in this study is similar to that observed in the present work, which also aligns with findings from other studies conducted in Brazil, characterized by a majority of male patients with an average age of 50 to 60 years[10, 11].

A study conducted at a philanthropic hospital in Rio Grande do Sul, comprising 49 beds, yielded results akin to the present study, with 24% of prescriptions containing antimicrobials[12]. However, there are reports in the literature indicating antimicrobial prescription rates exceeding 50%[10]. The observed difference may be related to the specialized nature of the hospital under study, which is focused on cardiology and does not provide emergency services. Additionally, excluding of the postoperative sector may contribute to the low rate of patients using antimicrobials.

The UpToDate® database served as the reference for analyzing treatment adequacy, contrasting with findings identified in the literature[10]. The National Guideline for the Development of Antimicrobial Stewardship Program emphasizes the importance of developing clinical protocols and their widespread dissemination to ensure uniformity of practice, adaptation to local realities, and ensuring that all healthcare professionals involved in patient care are aware of these protocols and can act as barriers to potential deviations, thus enabling a broader network for promoting the rational use of antimicrobials[1]. Developing protocols and expanding multidisciplinary team access represent feasible actions with positive potential for improving antimicrobial utilization in the study unit.

The antimicrobial consumption expressed in DDD per 100 patient days identified is consistent with other studies when evaluating the most used classes[13] and when assessing the consumption of the top ten antimicrobials regardless of class[14].

The presence of broad-spectrum antimicrobials among the top 10 most used in this study may be associated with a higher frequency of empirical treatments, the high frequency of sepsis as a clinical indication for use, and the reduced occurrence of de-escalation following the identification of the infectious agent and its susceptibility profile to antimicrobials.

The indicators associated with the duration of antimicrobial use (DOT and LOT) showed slightly lower values than those described in the literature[15,16]. A study comparing DOT in different hospital units also observed lower values in a cardiothoracic unit[15].

The observed clinical indications profile aligns with a study that identified pneumonia, surgical site infection, neutropenic fever, sepsis, and urinary tract infections as the most common treatment indications[17]. However, other authors have reported a higher frequency of indications such as lower respiratory tract pneumonia, intra-abdominal sepsis, bone infection, skin infection (including surgical site), and sepsis without clear focus[10].

In the literature, a higher frequency of empirically guided treatments (72%) was identified, followed by guided treatments (19.5%) and prophylactic treatments (8.5%)[18]. The predominance of empirically initiated treatments aligns with the results observed in the present study, although prophylactic treatments were more frequent than guided treatments. A possible explanation for the higher frequency of prophylactic treatments could be the need to prevent diseases related to bacterial infections with cardiac repercussions, given that patients with heart disease are at a higher risk for their development[19,20].

A pre-implementation study of ASP in a hospital in the United States[3] observed 43% inadequacy in the empirical use of antimicrobials, failure to de-escalate in 77% of applicable cases, and failure to discontinue inappropriate treatments in 48% of cases. These results differ from the findings identified in the present study, which showed lower inadequacy in the indication of empirical treatments and a higher frequency of de-escalation. However, the low frequency of discontinuation of inappropriate treatments was similar to that observed in another study[21], which also noted a low percentage of changes in treatments even with negative isolation results.

A post-implementation follow-up study of the ASP[5] identified 19% of treatments with incorrect indication, 17% with incorrect antimicrobial choice, 22% with inappropriate dosage, 13% with frequency, and 29% with duration. Another study[22], conducted at a pediatric hospital in the United

States from 2016 to 2017, observed non-conformities in 21% of prescriptions, with inappropriate antimicrobial choice being the most common, followed by the maintenance of surgical prophylaxis for more than 24 hours.

An assessment of the prophylactic use of antimicrobials in a hospital in the Philippines[23], from December 2013 to March 2014, found complete compliance in 13% of cases (indication, dose, route, and duration). Adequate antimicrobial selection occurred in 44% of cases, 39% had the appropriate dosage, 100% were administered via the correct route, and 67% had the correct duration.

The data presented regarding prophylactic treatments are consistent with the observation of a higher presence of errors related to the intended and actual duration of treatments analyzed in the present study. However, they differ in the low frequency of errors related to the choice of antimicrobial or prescribed dose for prophylactic treatments. This result may be related to the presence of an institutional protocol for prophylaxis.

The present study reported an 88% adequacy rate for prescribed dosage, with non-adjustment or inadequately adjusted dosage based on renal function being the primary reasons for inadequacy. A study conducted in the United States[24] assessed interventions performed between 2009 and 2012 in a hospital using the ASP. These interventions were related to incorrect dosage (39.0%), antimicrobial choice (20.5%), antimicrobial allergy (13.0%), and sequential therapy (11.5%). The authors also mention that these interventions had the potential to prevent the occurrence of 20.7% of potentially serious adverse events, which would represent a cost reduction of more than 6.5 million dollars.

In this scenario, despite a significant percentage of dosage adequacy, intensifying educational initiatives and promoting adjustment based on renal function can enhance antimicrobial utilization and, consequently, care safety.

An assessment of antimicrobial use according to the WHO's AWaRe classification in 69 countries[25] identified different distribution patterns across the three categories, with a higher proportion of antimicrobial utilization in the Watch category followed by the Access category in most countries. Similar findings were observed in other studies[26-28].

In the present study, not only was the Access category the least frequent, but the Reserve category accounted for 23.5% of prescribed antimicrobials. Although this pattern differs from that observed by other authors[25-28], it is consistent with the higher usage of Reserve category antimicrobials in Latin America (4.7%), with Brazil ranking third (7.1%) in this regard[25].

The cardiological profile of the unit under study may be associated with a higher prevalence of the use of Reserve-category antimicrobials, given that Daptomycin (the most utilized within the category) is one of the medications recommended by institutional protocol, UpToDate® and literature[29,30] for the treatment of IE, as well as sepsis and bloodstream infections resulting from IE. Nevertheless, this outcome underscores the importance of revising clinical practices to reduce the use of medications within this category in cases where substituting an antimicrobial from another category is applicable.

CONCLUSIONS

Despite the adoption of a retrospective data collection model, the selection of a few clinics from the hospital under study, and the limited period, which are the main limitations of this study, it was possible to identify a lower percentage of inadequacies in the use of antimicrobials compared to other studies described in the literature. However, the lack of traceability of all information associated with treatments, the absence or limited dissemination of institutional protocols, and the persistence of inadequacies in prescriptions for several days suggest the importance and opportunity for the development of an ASP and the involvement of pharmacists in this process.

The analysis of antimicrobial consumption patterns allowed the identification of critical areas to be addressed in the potential implementation of an ASP in the unit under study and by the pharmacy service team. Among these are de-escalating negative results, strengthening trust in the clinical laboratory, reducing empirical antimicrobial use, and seeking to expand the request for culture tests in these treatments. Actions aimed at addressing these challenges have great potential to achieve better clinical outcomes for patients, reduce adverse effects associated with inappropriate antimicrobial use, lower costs, and further the fight against antimicrobial resistance.

Another relevant aspect is the adoption and expansion of access for the multidisciplinary team to institutional guidelines, which can assist in better alignment of antimicrobial treatments regarding indication, dosage, and duration without requiring significant investments or changes in the unit's structure and routines.

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