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ORIGINAL ARTICLE

Care Bundle: Strategies for Managing Antimicrobials in a Reference Transplant Hospital in Northeastern Brazil

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ABSTRACT

Introduction: Infections by multidrug-resistant bacteria represent a serious public health problem, especially among transplant patients who, due to immunosuppression, become more susceptible to opportunistic infections and resistant pathogens. Antimicrobial Stewardship Programs (AMP) using care bundles have been implemented to promote the rational use of antibiotics and ensure care safety. **Objectives:** To evaluate the use of a care bundle in managing antimicrobial use in a transplant unit. **Methods:** This was an observational, descriptive, and retrospective study using data from the institutional AMP database. The antimicrobial management strategies employed between 2020, 2021, and 2023 were analyzed using a quantitative approach and statistical analysis. **Results:** A total of 398 patients were followed up, with 1,713 strategies recorded, of which 98.2% (n = 1,683) were accepted. The main strategy adopted was to reduce treatment time (30.8%). The most frequent treatment indications were bloodstream infection (47.2%) and upper respiratory tract infection (21.6%). Among the 1,390 antimicrobials monitored, 73.4% belonged to the therapeutic reserve category. Dose adjustment was associated with a 1.87-fold increase in the risk of death, a 5.37-fold increase in escalation, and a 2.33-fold increase in respiratory infections. Dose adjustment also increased treatment time by 10.4 days and hospitalization time by 13.4 days. Bloodstream infections, on the other hand, reduced treatment time by 9.5 days, which curiously increased hospitalization time by 5.2 days. **Conclusion:** The use of care bundles as part of AMP had a positive impact on the rational use of antimicrobials and relevant clinical outcomes, such as a reduction in the average length of stay and, consequently, exposure to antibiotics, with a possible reduction in resistance. However, mortality was associated with advanced age, the need for dose adjustment, escalation, and respiratory infections. Under-reporting and loss of data reinforce the need for digital technologies for real-time monitoring and continuous training of multi-professional teams.

Descriptors: Antimicrobial Stewardship; Pharmacy Service, Hospital; Drug Therapy; Transplantation.

Care Bundle: Estratégias para Gestão de Antimicrobianos em um Hospital Referência em Transplantes no Nordeste Brasileiro

RESUMO

Introdução: As infecções por bactérias multirresistentes representam um grave problema de saúde pública, especialmente entre pacientes transplantados que, devido à imunossupressão, tornam-se mais suscetíveis a infecções oportunistas e patógenos resistentes. Programas de Gerenciamento de Antimicrobianos (PGA), com uso de *care bundles*, têm sido implementados para promover o uso racional de antibióticos e garantir segurança assistencial. **Objetivos:** Avaliar a utilização de um pacote de cuidados (*care bundle*) na gestão do uso de antimicrobianos em uma unidade de transplante. **Métodos:** Estudo observacional, descritivo e retrospectivo, com dados extraídos do banco do PGA institucional. Foram analisadas as estratégias de manejo dos antimicrobianos empregadas entre os anos de 2020, 2021 e 2023, utilizando abordagem quantitativa e análise estatística. **Resultados:** Foram acompanhados 398 pacientes, com registro de 1.713 estratégias, das quais 98,2% (n = 1683) foram aceitas. A principal estratégia adotada foi a redução do tempo de tratamento (30,8%). As indicações de tratamento mais frequentes foram infecção de corrente sanguínea (47,2%) e trato respiratório superior (21,6%). Entre os 1.390 antimicrobianos monitorados, 73,4% pertenciam à categoria de reserva terapêutica. O ajuste de dose esteve associado ao aumento do risco de óbito em 1,87 vez, o escalonamento em 5,37 vezes e as infecções respiratórias em 2,33 vezes. O ajuste de dose também aumentou o tempo de tratamento em 10,4 dias e de internação em 13,4 dias. Já as infecções de corrente sanguínea reduziram o tempo de tratamento em 9,5 dias, o que, curiosamente, elevou o tempo de internação em 5,2 dias. **Conclusão:** O uso de *care bundles* como parte dos PGAs demonstrou impacto positivo no uso racional de antimicrobianos e em desfechos clínicos relevantes, como redução do tempo médio de internação e, consequentemente, da exposição a antibióticos, com possível diminuição da resistência. No entanto, a mortalidade esteve associada a idade avançada, necessidade de ajuste de dose, escalonamento e infecções respiratórias. A subnotificação e a perda de dados reforçam a necessidade de tecnologias digitais para monitoramento em tempo real e capacitação contínua das equipes multiprofissionais.

Descritores: Gestão de Antimicrobianos; Serviço de Farmácia Clínica; Farmacoterapia; Transplante.

INTRODUCTION

Healthcare-related infections (HAIs) caused by multidrug-resistant bacteria represent a serious public health problem and are often associated with high mortality rates, challenges in infection prevention and control, and scarce therapeutic options. Among the strategies recommended to deal with this problem are the development and implementation of programs for the rational use of antimicrobials, known as Antimicrobial Stewardship Programs (ASPs), which aim at the early adaptation of antimicrobial therapy through individual assessment of cases by infection control specialists.[1]

Accordingly, the National Health Surveillance Agency, in line with the goals of the World Health Organization's Global Action Plan and the Brazilian Program for the Prevention and Control of Healthcare-Related Infections, published in 2023 the latest version of the National Guideline for the Elaboration of an Antimicrobial Use Management Program in Health Services, including updates on the guidelines for the elaboration and implementation of ASPs in Brazilian health services, in addition to including new scientific evidence and recommendations from national and international bodies, adapted to the Brazilian context.[2]

Based on the assumptions of this guideline, the teaching hospital where this study was carried out has a well-established institutional policy on the use of PGA as an essential part of the provision of health care, which is part of the services offered and managed by the Hospital Infection Control Commission (HICC), with a wide range of scientific publications with robust results from the optimization of antimicrobial pharmacotherapy, interdisciplinary action, and cost minimization.

In this scenario, therapeutic reserve antimicrobials include high-cost items with a broad spectrum, greater toxicity, and more inducers of antimicrobial resistance (AMR). For their use, a request and preauthorization form from the operational team must be completed, and they should be reserved for the treatment of confirmed or suspected infections due to multi-resistant organisms and treated as "last resort" options. Strategic therapies, on the other hand, can be optimized, such as oral sequential therapy, due to their good bioavailability profile (above 80%), lower financial cost, and greater convenience of use.[3]

Antimicrobial stewardship seeks to optimize clinical results and reduce unwanted events related to the inappropriate use of antimicrobial therapy. They play a fundamental role in managing bacterial resistance, and their main strategy is to administer the right antimicrobial to the right patient, at the right dose, and at the right time. According to the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America, the collaboration between an infectious disease physician and a clinical pharmacist, as well as other healthcare professionals, improves clinical outcomes by conducting prospective audits/feedback, using restriction forms, educating professionals, and implementing evidence-based guidelines[4]. As part of the ASP team, the clinical pharmacist is responsible for evaluating medical prescriptions, monitoring the results of laboratory tests, following institutional protocols, and carrying out interventions relevant to the use of antimicrobials, such as de-escalation and escalation, dose optimization, and switching from intravenous to oral therapy.[5]

To this end, the development and use of a care bundle for antibiotic therapy management is an important tool to guide the conduct of the professionals involved, contributing to patient safety by systematizing care. A care bundle consists of an articulated methodology developed to improve the processes and results of patient care, proposed by the Institute for Healthcare Improvement and based on scientific evidence, constituting a set of simple and cost-effective interventions, which the team should apply methodically in all phases of health care with the aim of reducing adverse events.[6,7]

With regard to patients undergoing solid organ transplantation, developments in immunosuppressive therapy have been effective in reducing the incidence of rejection. However, it is worth noting that vulnerability to opportunistic infections and multidrug-resistant pathogens remains a significant complication with a relevant impact. The main infections are often related to the surgical site, bloodstream, and respiratory and urinary tracts. These complications are generally associated with the severity profile of the patients, invasive procedures, immunosuppressants, prolonged hospitalization, colonization by resistant microorganisms, indiscriminate use of antimicrobials, and the hospital environment, which favors the natural selection of microorganisms. Given the seriousness of HAIs and their potential adverse consequences, identifying these infections and the factors that are associated with them is of the utmost importance and can provide valuable input for the development of strategies for the prevention, screening, diagnosis, and treatment of these complications, thus helping to improve post-transplant survival.[8]

Therefore, the aim of this study was to evaluate the utilization of a care bundle to manage the use of antimicrobials in a transplant unit. Thus, it is hoped that this research will contribute to scientific progress and, in the future, promote improvements in the quality of health care, as well as allow its effectiveness to be evaluated.

METHODS

Study design, population, location, and period

This is a descriptive, retrospective, cross-sectional study with the aim of evaluating the use of a care bundle in the management of antimicrobial use in patients receiving solid organs.

The research was carried out at the Walter Cantídio University Hospital, located in Fortaleza, Ceará. The educational institution, which is part of the Unified Health System, offers highly complex quaternary health care, has a federal administrative sphere, and stands out as a reference center for transplants, encompassing continuous training of human resources and promoting research in the area of health. The solid organ transplant unit has 22 beds, divided between the kidney transplant ward (13 beds) and the liver transplant ward (9 beds), and has a team of medical assistants and residents, nurses, nursing technicians, pharmacists, psychologists, nutritionists, and social workers. The transplant service also has two outpatient clinics (kidney and liver transplants), where patients are monitored during the pre- and post-transplant periods.

The population was composed of patients hospitalized in the solid organ transplant unit using antimicrobials and who were monitored by the ASP during the years 2020, 2021, and 2023.

Data collection and variables studied

The data were extracted from a Google Spreadsheets database stored at the HICC of the hospital in this study, which manages the ASP data fed by the pharmacy interns of the aforementioned program. The variables evaluated included antimicrobial management strategies and acceptance percentages, as well as antimicrobial classes prescribed, infection topography, clinical outcome, reserve and/or strategic antimicrobials, number of patients followed up, number of antimicrobials monitored, average hospitalization time, average treatment time, average age, and discharge/death outcomes.

The ASP database contained a record of the antimicrobial management strategies carried out on physical monitoring forms by the institution's professionals (in the case of three or more strategies per antimicrobial, only the two with the greatest economic impact were considered for incorporation into the database), which also contained the names of the drugs involved with their respective classes, treatment time, dates of dose adjustments, treatment indication, topography, place of prescription, request for antimicrobial record and opinion of the HICC, cultures requested, adequacy of the therapy of choice, patient identification (initials of name, medical record) and history of current illness (including comorbidities), previous hospitalization, previous use of antimicrobials, and clinical outcome of the patient (discharge, transfer, or death), as well as containing space to inform the date of hospitalization and discharge, allowing a quantitative evaluation of the data.

The institutional ASP antimicrobial therapy monitoring tool used by the clinical pharmacists at the solid organ transplant service where the study was conducted includes demographic data and the patient's health history, as well as space to record the daily monitoring of antimicrobial use, including the strategies of the ASP team, which are part of the care bundle for managing antimicrobial use. The bundle of strategies listed in the ASP includes:

- Escalation: broadening the antimicrobial spectrum against a larger group of bacterial species[9]. Example: substitution of piperacillin+tazobactam for meropenem;
- De-escalation: reduction of the antimicrobial's spectrum of action guided by the microorganism's sensitivity profile, reducing the possibility of generating bacterial resistance[9]. Example: replacing meropenem with piperacillin+tazobactam;
- Completion of treatment: completion of treatment within the timeframe initially proposed, respecting the minimum and maximum time provided. Example: finishing a treatment within 7 to 10 days of taking the antimicrobial;
- Reduced treatment time: ending treatment in fewer days of use. Example: ending treatment on the 5th day of use, when the forecast was 7 to 10 days, after a negative culture or clinical and laboratory improvement of the patient;
- Extended treatment time: complete the treatment over a longer number of days. Example: ending treatment on the 14th day of use, when the forecast was 7 to 10 days after the culture remained positive;
- Oral sequential therapy: converting the therapy of the same antimicrobial from intravenous to oral use[10]. Example: substitution of linezolid solution for oral tablet;

- Switch: conversion of one antimicrobial to another of the same class but a different compound with similar potency[11,12]. Example: switching vancomycin for teicoplanin due to the greater nephrotoxicity of the former;
- Step down: simplification of antimicrobial therapy to one with a lower spectrum of action than the initial therapy, providing greater therapeutic convenience for the patient[13]. Example: exchange between meropenem (3× a day) and ertapenem (1× a day, it does not cover *Pseudomonas aeruginosa* or *Acinetobacter baumannii*) with the aim of de-hospitalizing the patient so that they can finish their treatment on an outpatient basis in a day hospital, culminating in the practice of outpatient parenteral antimicrobial therapy, which consists of an alternative for reducing hospitalization time and increasing therapeutic convenience for the patient[14];
- Dose optimization: adjusting the dose of the antimicrobial to the type of infection or the patient's clinical condition, considering the severity of the condition. Example: optimizing the dose of meropenem from 1 g 8/8 h to 2 g 8/8 h.
- Dose adjustment: changing the dose of the antimicrobial according to the optimal dose for kidney function (according to creatinine clearance) or serum level (such as in monitoring vancomycin). Example: meropenem dose adjustment from 1 g 8/8 h to 1 g 12/12 h due to a clearance of 38 mL/min/1.73 m^2;
- Serum monitoring: measurement and interpretation of the antimicrobial's serum levels in order to determine the necessary individualized doses that guarantee effective and safe plasma concentrations[15]. Example: monitoring vancomycin;
- Culture request: request for the collection of cultures to monitor therapeutic efficacy and identify the pathogen;
- Request form: asking the medical team to fill in the request form for reserve and/or strategic antimicrobials containing the justification for the treatment and the proposed duration, which will be evaluated by the HICC for the release or not of the treatment and suggestions made if necessary.

At the hospital in this study, reserve antimicrobials included liposomal amphotericin B, anidulafungin, daptomycin, ertapenem, imipenem+cilastatin, linezolid, meropenem, micafungin, polymyxin B, teicoplanin, tigecycline, vancomycin, ceftolozane/tazobactam, or ceftazidime/avibactam. The strategic ones are composed of levofloxacin, ciprofloxacin, fluconazole, voriconazole, clindamycin, or metronidazole.

Inclusion criteria

The study included all patients undergoing kidney and liver transplantation admitted to the transplant unit of the study hospital, of both sexes, of varying ages, and who used reserve and/or strategic antimicrobials during 2020, 2021, and 2023.

Exclusion criteria

The exclusion criteria for the study were patients who were not using antimicrobials and were therefore not followed up by the ASP, patients followed up in 2022 because there were no data from that period in the ASP database, and patients admitted to hospitalization units other than the transplant.

Data analysis

The data extracted from the ASP database was stored in a separate database in the Google Spreadsheets software and then analyzed quantitatively by descriptive analysis of the numerical variables, using simple mean and standard deviation. Categorical variables were expressed as frequencies, and prevalence rates as percentages.

Statistical analysis

Statistical analyses were carried out using IBM SPSS software version 22. The normality of the numerical variables was checked using the Shapiro–Wilk test. The distributions of the categorical variables were checked using the chi-square (χ^2) and Fisher's exact tests, expressed in absolute (N) and relative (%) forms. Continuous quantitative variables were compared using the Mann–Whitney test, expressed as a median (25% quartile – 75% quartile). The prediction analyses were checked by linear regression and binary logistic regression. The criterion for statistical significance was $p < 0.05$.

The outcomes analyzed were:

- Comparison of the distributions of age, length of treatment, and length of hospitalization according to discharge and death outcomes;
- Distribution of specialties, strategies, infection topographies, and antibiotic classifications according to discharge and death outcomes;
- Prediction of risk of death;
- Prediction of treatment and hospitalization time.

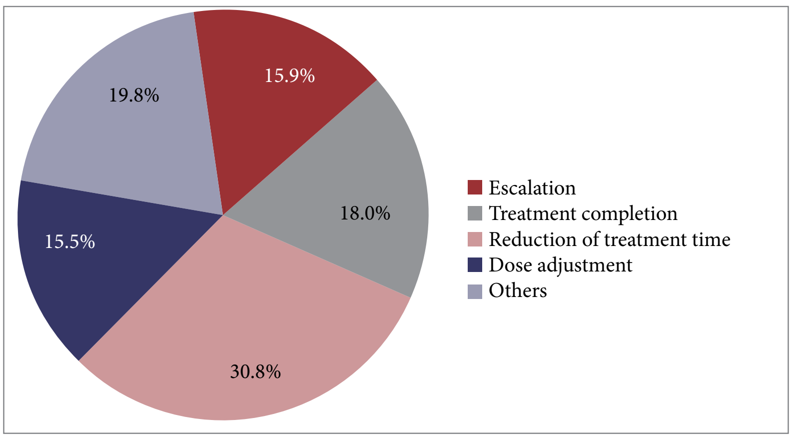
Ethical aspectss

This study did not involve interviews with patients, so there was no need for an informed consent form. The project was approved by the Research Ethics Committee of the Federal University of Ceará / Walter Cantídio University Hospital, under opinion number 5.409.579 and CAAE 56178022.9.0000.5045, in accordance with Resolution 466 of the National Health Council of the Ministry of Health, considering respect for human dignity and the special protection due to participants in scientific research involving human beings.

RESULTS

With regard to the strategies that the ASP team carried out during the monitoring of antimicrobial treatments in the period under analysis (2020, 2021, and 2023), 1,713 proposed strategies were identified, with a distribution of 886 (51.72%) strategies in kidney transplantation and 827 (48.28%) in liver transplantation, 98.2% of which were accepted (n = 1,683).

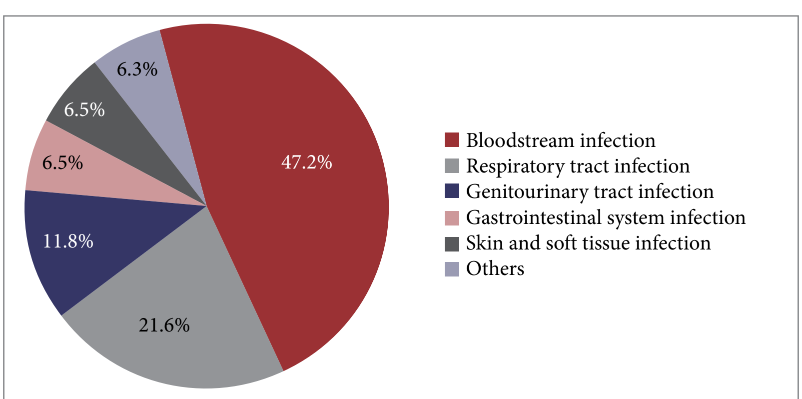
Among these, the most frequently used can be listed: reducing treatment time (30.8%), ending treatment (18.0%), escalation (15.9%), dose adjustment (15.5%), dose optimization (5.2%), prolonging treatment (4.7%), de-escalation (3.5%), and serum monitoring (3.0%). The switch and oral sequential therapy strategies accounted for only 1.8% and 0.7% of the total performed, respectively. The strategies are described with their representativeness and category in Fig. 1.



Source: Prepared by the authors based on the institution's PGA database.

Figure 1. Main strategies proposed in the ASP.

In addition, with regard to the indication of the proposed treatment, various types of infections were identified, which are divided by system or topography on the monitoring form. They are: undetermined focus, bloodstream infection, skin and soft tissue infection, central nervous system infection, surgical site infection, osteoarticular tissue infection, cardiovascular system infection, gastrointestinal system infection, genitourinary tract infection, respiratory tract infection, infection of the eyes, ears, nose, throat, and mouth, and infection in prostheses and other devices. Among them, those with the highest prevalence were: bloodstream infection (47.2%), respiratory tract infection (21.6%), genitourinary tract infection (11.8%), gastrointestinal system infection, and skin and soft tissue infection (6.5% each). Figure 2 illustrates these data.



Source: Prepared by the authors based on the institution's PGA database.

Figure 2. Distribution of types of infections by system or topography expressed as a percentage (n = 398).

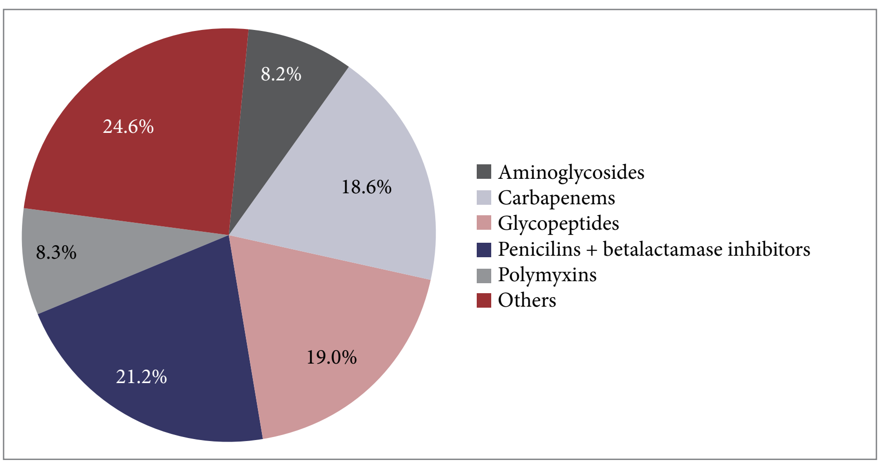
In 2020, 2021, and 2023, 1,390 prescribed antimicrobials were monitored by the ASP, of which 1,020 (73.38%) were therapeutic reserves and 158 (11.37%) were strategic. A total of 683 prescribed antimicrobials were monitored in the liver transplant unit in 2020, 2021, and 2023. The number of kidney transplants was 707 in the same period. Table 1 shows the data obtained.

Table 1. Total number of antimicrobials monitored by the ASP.

Total number of antimicrobials monitored by the ASP	
Specialty	**Total**
Liver transplant	683
Kidney transplant	707
	1,390

Source: Prepared by the authors based on the institution's PGA database.

Among the most prescribed classes of antimicrobials were penicillins in association with beta-lactamase inhibitors (21.2%), with piperacillin+tazobactam as the representative; glycopeptides (19%), including linezolid, teicoplanin, and vancomycin; carbapenems (18.6%), with meropenem as the most prescribed item; polymyxins (8.3%) B and E; and aminoglycosides (8.2%), with amikacin and gentamicin as representatives. In addition to these groups, other classes of antimicrobials were prescribed, including antivirals, benzimidazoles, cephalosporins (1st, 2nd, 3rd, and 4th generations, including 3rd-generation cephalosporins in association with beta-lactamase inhibitors), echinocandins, glycylcyclines, imidazoles, lincosamides, lipopeptides, macrolides, monobactams, penicillins, polyenes, quinolones, and triazoles (1st and 2nd generations). This information is shown in Fig. 3.



Source: Prepared by the authors based on the institution's PGA database.

Figure 3. Most prescribed antimicrobial classes (n = 1,390).

During the study period, 398 patients admitted to the solid organ transplant unit were monitored by the ASP, of which 176 (44.2%) were liver transplant patients and 222 (57.8%) were kidney transplant patients. The quantity of patients is understood to be the number of antimicrobial monitoring records, and the same patient may have multiple hospitalizations, thus having different records. This data is shown in Table 2.

Table 2. Distribution of the number of ASP patients by specialty (liver and kidney transplant).

Specialty	Number of patients by specialty			
	Years evaluated N (%)			
	2020	**2021**	**2023**	**Total**
Liver transplant	1 (0.57%)	158 (89.77%)	17 (9.66%)	176
Kidney transplant	69 (31.08%)	116 (52.25%)	32 (14.41%)	222
				398

Source: The institution's ASP database.

The patients ranged in age from 16 to 89, with a mean of 52 ± 17 years. In total, 98 (24.6%) patients died during hospitalization. The average length of hospital stay for patients undergoing a liver transplant was 67 days in 2020 (data were found for only 1 patient follow-up in that year, who was hospitalized for 67 days due to multiple complications), 32.08 days in 2021, and 18.82 days in 2023. In the kidney transplant unit, patients had an average length of stay of 33.51 days in 2020, 32.16 days in 2021, and 21.66 days in 2023 (Table 3).

Table 3. Average length of hospital stay of patients monitored by the ASP shown in days and by specialty (liver and kidney transplant).

Specialty	Average length of hospital stay in days		
	Years evaluated		
	2020	2021	2023
Liver transplant	67.0	32.08	18.82
Kidney transplant	33.51	32.16	21.66

Source: Prepared by the authors based on the institution's PGA database.

According to Table 4, the average treatment time for ASP patients in the liver transplant unit was 37.00 days in 2020, 26.23 days in 2021, and 17.88 days in 2023. In kidney transplantation, the average number of days was 28.70 in 2020, 24.44 in 2021, and 20.09 in 2023.

Table 4. Average treatment time for ASP patients shown in days and by specialty (liver and kidney transplant).

Specialty	Average treatment time in days		
	Year		
	2020	2021	2023
Liver transplant	37.00	26.23	17.88
Kidney transplant	28.70	24.44	20.09

Source: Prepared by the authors based on the institution's PGA databas

When checking for differences between age, treatment times, and hospitalization according to the outcomes of discharge and death, it was observed that higher age and shorter treatment times were associated with the outcome of death, as shown in Table 5.

Table 5. Comparison of the distributions of age, length of treatment, and length of hospitalization according to discharge and death outcomes.

Variables	Discharge Median [25%–75%]	Death Median [25%–75%]	*p*
Age (years)	51 [37–63]	61 [51–70]	**< 0.001**
Treatment time (days)	14 [9–25]	11 [4–23]	**0.010**
Length of stay (days)	23 [16–36]	26 [16–45]	0.234

Mann–Whitney test; Significance $p < 0.05$. Source: Prepared by the authors based on the institution's PGA database.

After excluding 20 patients who dropped out of follow-up, the association of specialties, strategies, infection topographies, and antibiotic classifications with discharge and death outcomes was analyzed. It was observed that, among the strategies, the need for dose adjustment and escalation was associated with a higher frequency of death. As for the topography of the infection, respiratory tract infections were associated with a higher frequency of death. The specialties and classifications of antibiotics were not associated with the outcomes analyzed, as shown in Table 6.

When analyzing the risk of death by binary logistic regression, it was observed that the need for dose adjustment presented a significant model [χ^2 (1) = 6.535; p = 0.011; $R^2_{Nagelkerke}$ = 0.026], as well as the need for escalation [χ^2 (1) = 42.3; $p < 0.001$; $R^2_{Nagelkerke}$ = 0.16] and respiratory tract infections [χ^2 (1) = 9.8; p = 0.002; $R^2_{Nagelkerke}$ = 0.039]. The need for dose adjustment was found to increase the risk of death by 1.87 times (1.1–3.0), escalation by 5.37 times (3.1–9.2), and respiratory tract infection by 2.33 times (1.3–3.9), as shown in Table 7.

Table 6. Distribution of specialties, strategies, infection topographies, and antibiotic classifications according to discharge and death outcomes.

Variables			Discharge N = 290 (%)	Death N = 88 (%)	*p*
Specialties		Liver	133 (45.9%)	42 (47.7%)	0.759[a]
		Kidneys	157 (54.1%)	46 (52.3%)	
Strategies	Dose adjustment	Yes	107 (36.9%)	*46 (52.3%)**	**0.010[a]**
		No	183 (63.1%)	42 (47.7%)	
	Escalation	Yes	108 (37.2%)	*67 (76.1%)**	**< 0.001[a]**
		No	182 (62.8%)	21 (23.9%)	
	Treatment reduction	Yes	188 (64.8%)	56 (63.6%)	0.838[a]
		No	102 (35.2%)	32 (36.4%)	
Topography	Bloodstream	Yes	102 (35.2%)	29 (33%)	0.702[a]
		No	188 (64.8%)	59 (67%)	
	Respiratory tract	Yes	57 (19.7%)	*32 (36.4%)**	**0.001[a]**
		No	233 (80.3%)	56 (63.6%)	
		Reserve	266 (91.7%)	86 (97.7%)	
Antibiotic classifications		Strategic	17 (5.9%)	1 (1.1%)	0.130[b]
		Other	7 (2.4%)	1 (1.1%)	

[a]Chi-square test (χ^2); [b]Fisher's exact test; Significance $p < 0.05$; (italics)*: Frequency statistically different from expected; Bold: $p < 0.05$. Source: Prepared by the authors from the institution's ASP database.

Table 7. Prediction of risk of death.

Predictors	Beta	Standard error	*Odds Ratio*	p	CI 95%
Dose adjustment	0.628	0.246	1.87	**0.011**	1.1–3.0
Escalation	1.682	0.278	5.37	**< 0.001**	3.1–9.2
Respiratory tract	0.848	0.266	2.33	**0.001**	1.3–3.9

Binary logistic regression; 95% CI: 95% confidence interval; Significance (bold): $p < 0.05$. Source: Prepared by the authors from the institution's ASP database.

In order to verify the impact of specialties, strategies, infection topographies, and antibiotic classifications on treatment and hospitalization periods, two linear regression models were carried out with all the variables, of which the following were significant: treatment period [$\chi^2(7, 377) = 7.9$; $p < 0.001$; $R^2_{adjusted} = 0.114$] and length of stay [$\chi^2(7, 377) = 6.69$; $p < 0.001$; $R^2_{adjusted} = 0.096$]. It was observed that, in relation to treatment time, the need for dose adjustment predicted an increase of 10.4 days; in contrast, bloodstream infections predicted a reduction of 9.5 days. With regard to length of stay, the need for dose adjustment predicts an increase of 13.4 days, and the need to reduce treatment predicts an increase of 5.2 days, as shown in Table 8.

Table 8. Prediction of treatment and hospitalization time.

Variables		Beta	Standard error	*p*	CI 95%
Dependents	Independents				
Treatment	Dose adjustment	10.4	1.90	**< 0.001**	6.68–14.10
	Bloodstream	–9.5	2.17	**< 0.001**	(–13.70)–(–5.20)
Hospitalization	Dose adjustment	13.4	2.54	**< 0.001**	8.40–18.40
	Treatment reduction	5.2	2.66	**0.049**	0.02–10.40

Note: Linear regression; 95% CI - 95% confidence interval; Significance (bold): $p < 0.05$. Source: Prepared by the authors from the institution's ASP database.

DISCUSSION

A highlight of this study was the impact of the strategies proposed by the ASP. Among the 1,713 strategies applied, reducing treatment time was the most frequent (30.8%), followed by treatment termination (18%), escalation (15.9%), and dose adjustment (15.5%). These interventions are consistent with the IDSA recommendations, which point out the importance of adjusting the time and antimicrobial spectrum according to the patient's clinical profile in order to avoid bacterial resistance.[16]

Another relevant finding was the consistent reduction in the average length of hospital stay over the years analyzed. In liver transplantation, the average time fell from 67 days in 2020 to 18.8 days in 2023. Similarly, in kidney transplantation, there was a reduction from 33.5 days to 21.7 days over the same period. This trend suggests that improved antimicrobial management practices, combined with the continuous use of the care package, contribute to early hospital discharge, reducing prolonged exposure to the hospital environment and, consequently, the risk of HAIs.[6]

In addition, it was shown that, during the first year of the COVID-19 pandemic (2020), the number of patients monitored by the ASP was lower compared to other years, given the need for social distancing, reduction of human resources, and activities commonly carried out in the routine of the institution's professionals. On the other hand, in 2021, there was a significant increase in the number of patients followed up by the ASP. Another study revealed similar results, reporting that in 2021 there was a gradual progression in the ASP bed coverage rate at its study hospital after a drop in this rate the previous year.[17]

The most prescribed antimicrobial classes, including penicillins with beta-lactamase inhibitors (21.2%), glycopeptides (19%), and carbapenems (18.6%), reinforce the need for continuous surveillance in transplant patients. These classes, often associated with the management of serious infections, are also known for their risk of inducing resistance when used indiscriminately. The registration of 73.38% of antimicrobials as therapeutic reserves shows a strategic focus on rational use but also points to the complexity of the cases treated.[9]

The main types of infections transmitted—bloodstream (47.2%), respiratory tract (21.6%), and genitourinary tract (11.8%)—are consistent with the literature, which associates bloodstream and respiratory infections with higher morbidity and mortality rates in immunosuppressed patients[8]. The ASP's systematic approach to requesting cultures and monitoring the microbiological profile was fundamental for the early identification of pathogens and therapeutic adjustments, and 98.2% of the proposed strategies were accepted by the medical team.

The implementation of strategies such as de-escalation, dose optimization, and therapeutic monitoring, demonstrated in this study, is in line with global practices proven to be effective in controlling adverse drug reactions and improving clinical outcomes[18]. Meanwhile, over the years it has been shown that strategies such as reducing treatment time and dose adjustment can generate significant savings by reducing the length of stay and the costs associated with prolonged hospitalizations, a reflection of the continuous improvement of ASP practices.[19,20]

A recent study highlighted that the large-scale use of antimicrobials, without adequate criteria, is one of the main factors behind the increase in AMR rates. In a global analysis, ASPs have significantly reduced the prevalence of HAIs, above all by limiting the use of broad-spectrum antibiotics and optimizing treatment time through precise adjustments in therapy[21]. In the context of transplantation, this is particularly relevant, since immunosuppressed patients are at greater risk of contracting serious infections caused by multidrug-resistant pathogens.

A meta-analysis revealed that the use of ASPs in hospitals resulted in a 33.9% reduction in total antimicrobial costs and a reduction in the length of hospital stay. These programs have also been associated with a reduction in infections by resistant pathogens, without increasing mortality[22]. In another study conducted in a community hospital in Italy, the implementation of an ASP led to a 35% reduction in antimicrobial-related costs per patient, as well as improvements in clinical and microbiological outcome measures.[23]

The Brazilian Health Surveillance Agency[2] points out that the implementation of ASP aims to optimize the use of antimicrobials in health services and offers direct benefits to patients, guaranteeing the desired therapeutic effect and minimizing the occurrence of adverse events associated with the use of antimicrobials, such as nephrotoxicity. Strategies such as therapeutic monitoring of antimicrobials, exemplified by monitoring plasma levels of vancomycin, are crucial to ensure safe and effective plasma concentrations, preventing serious complications. Vancomycin is widely used in the treatment of methicillin-resistant *Staphylococcus aureus* infections; however, due to its nephrotoxic potential, serum monitoring is essential to adjust doses and avoid renal toxicity.[24]

On the other hand, statistical analysis showed that the outcome of death was related to higher age and shorter treatment time. The study by Chen et al.[25] investigated the relationship between age and the risk of mortality in liver transplant recipients. The results indicated that older patients, especially those undergoing dialysis, have a higher mortality rate, possibly due to the presence of comorbidities. The study by Choi et al.[26] identified advanced age as an independent risk factor for treatment-related mortality in kidney transplant recipients. However, regarding the duration of antimicrobial treatment, the study by Avni-Nachman et al.[27] compared short- and long-term antibiotic treatments for complicated urinary tract infections in kidney transplant recipients. The results indicated that the duration of treatment is not associated with significant differences in clinical outcomes, including mortality or readmissions, suggesting that the duration of antimicrobial treatment may not be a critical factor for mortality in kidney transplant patients in their study.

In addition, a study conducted by Zilberberg et al.[28], which investigated the relationship between the escalation of antimicrobial therapy and hospital mortality in patients with healthcare-associated pneumonia, showed that inadequate initial empirical treatment was associated with higher hospital mortality, especially in non-bacteremic patients. Subsequent escalation of therapy did not attenuate the risk of death, suggesting that the inadequate initial choice of antibiotics almost tripled the risk of hospital mortality. These findings highlight the complexity of antimicrobial management in severe respiratory infections and the importance of an appropriate initial choice of antibiotics to improve clinical outcomes. The decision to adjust or escalate the dose should be carefully considered based on specific clinical factors and the patient's response to the initial treatment.

Even so, the study foresees weaknesses, such as underreporting, loss of follow-up in patient monitoring, and loss of data in the ASP database, especially in 2022. The great variability in the number of follow-ups per year/specialty is a limitation that can lead to false conclusions regarding the downward trend in hospitalization time. These factors compromise the accurate analysis of longitudinal indicators and reinforce the need for integrated digital systems to record in real-time, as suggested by Barros[1]. The literature suggests that the use of digital technologies to track antibiotic administration and the integration of advanced digital systems, such as artificial intelligence platforms, can significantly improve real-time data collection and analysis, allowing for faster and more effective therapeutic adjustments, thus improving clinical outcomes. It also highlights the need for continuous training of multi-professional teams and the strengthening of data collection tools to ensure greater reliability. Therefore, as practices evolve, the use of resources such as prescription audits, continuous feedback, and the integration of new digital technologies should be prioritized to maximize benefits and face emerging challenges, promoting more effective and sustainable management in the fight against AMR and improving quality of care, especially in hospitals with limited resources.

CONCLUSION

The application of strategies in the ASP has shown over the years a positive impact on both patients and healthcare institutions, in addition to cost savings. This study has demonstrated the relevance of the use of care bundles as part of ASPs in improving clinical outcomes and the effective control of AMR, especially in immunosuppressed populations such as transplant patients, as well as contributing to the education of the prescribing professional when prescribing and monitoring antimicrobial therapy, generating feedback on prescription time, antimicrobial use time, and acceptance of the strategies recommended by the clinical pharmacist.

In addition, the strategies applied, such as reducing treatment time, treatment completion, and dose adjustment, revealed a possible positive impact on reducing the average length of stay and the rational use of broad-spectrum antimicrobials, promoting a more targeted and safer approach to infection management, corroborating data from recent literature on the efficacy of ASPs in controlling AMR and preventing HAIs.

On the other hand, statistical analysis found that death was associated with older age, shorter treatment time, need for dose adjustment, escalation, and respiratory tract infections. As for the strategies, dose adjustment increases the risk of death by 1.87 times and escalation by 5.37 times. In terms of topography, respiratory tract infections increase this risk by 2.33 times. Treatment time is influenced by the need to adjust the dose, increasing treatment time by 10.4 days; in contrast, bloodstream infections reduce treatment time by 9.5 days. With regard to hospitalization time, dose adjustment increases by 13.4 days, and treatment reduction increases by 5.2 days.

Finally, this study contributes to the rational use of antimicrobials by demonstrating the applicability and benefits of care packages, a model that can be replicated in other healthcare facilities. In addition, the evidence generated can provide public subsidies for the formulation of policies and the integration of digital technologies into antimicrobial monitoring systems, promoting greater precision and efficiency in management and corroborating previous research results, which show that the use of care bundles promotes greater adherence to good practices and better clinical and economic outcomes.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantial scientific and intellectual contributions to the study: Ruivo AKP, Oliveira AB; **Conception and design:** Ruivo AKP, Oliveira AB; **Data analysis and interpretation:** Ruivo AKP, Oliveira AB, Costa MDR; **Article writing:** Ruivo AKP, Oliveira AB, Costa MDR; **Critical review:** Ruivo AKP, Oliveira AB, Costa MDR; **Final approval:** Ruivo AKP, Oliveira AB, Costa MDR.

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