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IMPLICATIONS OF ANTIMICROBIAL STEWARDSHIP IN A PUBLIC HOSPITAL

IMPLICAÇÕES DO GERENCIAMENTO DE ANTIMICROBIANOS EM UM HOSPITAL PÚBLICO

IMPLICACIONES DE LA ADMINISTRACIÓN DE ANTIMICROBIANOS EN UN HOSPITAL PÚBLICO

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ABSTRACT
To describe the clinical and financial implications of the strategies of an Antimicrobial Stewardship Programme (AMP) in the adult and paediatric wards and Intensive Care Units (ICUs) of a public hospital in the state of Ceará. This was a prospective, descriptive and quantitative study of the implications of the recommendations made by the AMP team between June and October 2023. Data was collected from electronic medical records and patient files monitored by the programme. The clinical significance, acceptability rate and minimised cost of the recommended strategies were analysed. 1165 recommendations were made in 553 patients, with stopping treatment (25.24%) being the most common type of recommendation, followed by dose adjustment (22.83%). Reducing unnecessary exposure to antimicrobials (42.40 per cent) and increasing treatment efficacy (32.79 per cent) stood out as the most common clinical impacts. Recommendations were the most important in 50.47 per cent of cases. The minimising strategies resulted in net cost savings of approximately R$115,843.75. The team's recommendations had a positive influence on both the clinical and financial results of antimicrobial use.
Keywords: *Health Management; Health Strategies; Public Hospitals.*

RESUMO
Descrever as implicações clínicas e financeiras das estratégias de um Programa de Gerenciamento de Antimicrobianos (PGA) nas enfermarias e Unidades de Terapia Intensiva (UTIs) adultas e pediátricas de um hospital público do estado do Ceará. Trata-se de um estudo prospectivo de abordagem descritiva e quantitativa das implicações sobre as recomendações da equipe do PGA no período de junho a outubro de 2023. Os dados foram coletados através dos prontuários eletrônicos e fichas dos pacientes acompanhados pelo programa. Foram analisados, o significado clínico, a taxa de aceitabilidade e o custo minimizado das estratégias recomendadas. Foram realizadas 1165 recomendações em 553 pacientes, sendo, o fim do tratamento (25,24%), o tipo de recomendação mais comum, seguida do ajuste de dose (22,83%). A redução da exposição desnecessária a antimicrobianos (42,40%) e o aumento da eficácia do tratamento (32,79%) destacaram-se como impactos clínicos mais comuns. As recomendações foram de maior importância em 50,47% dos casos. As estratégias minimizadoras se traduziram em uma economia de custos líquida de aproximadamente R$ 115.843,75. As recomendações da equipe influenciaram positivamente tanto nos resultados clínicos quanto financeiros no uso de antimicrobianos.
Descritores: *Gestão em Saúde; Estratégias de Saúde; Hospitais Públicos.*

RESUMEN
Describir las implicaciones clínicas y financieras de las estrategias de un Programa de Manejo Antimicrobiano (PMA) en las salas de adultos y pediátricas y Unidades de Cuidados Intensivos (UCI) de un hospital público en el estado de Ceará. Se trató de un estudio prospectivo, descriptivo y cuantitativo de las implicaciones de las recomendaciones realizadas por el equipo del PAM entre junio y octubre de 2023. Los datos se recogieron de las historias clínicas electrónicas y de los expedientes de los pacientes monitorizados por el programa. Se analizó la importancia clínica, la tasa de aceptabilidad y el coste minimizado de las estrategias recomendadas. Se realizaron 1165 recomendaciones en 553 pacientes, siendo la interrupción del tratamiento (25,24%) el tipo de recomendación más frecuente, seguida del ajuste de dosis (22,83%). La reducción de la exposición innecesaria a los antimicrobianos (42,40%) y el aumento de la eficacia del tratamiento (32,79%) destacaron como las repercusiones clínicas más comunes. Las

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recomendaciones fueron las más importantes en el 50,47% de los casos. Las estrategias minimizadoras supusieron un ahorro neto de costes de aproximadamente 115.843,75 reales. Las recomendaciones del equipo tuvieron una influencia positiva tanto en los resultados clínicos como financieros del uso de antimicrobianos.
Descriptores: *Gestión en Salud; Estrategias de Salud; Hospitales Públicos.*

INTRODUCTION

Antimicrobial agents comprise a drug class with antibacterial, antifungal, antiparasitic, and antiviral activity. The use of this class has been carried out inadequately, excessively and empirically, with clinical and financial implications for the public health system. Adverse reactions and/or death, treatment failure, prolonged hospital stay, increased antimicrobial resistance (AR) and greater use of hospital resources are among the consequences of the irrational use of these drugs[1].

The rise of AR has had a profound impact on global health and the economy. According to the World Health Organization (WHO), if action is not taken, it is estimated that by 2050 the problem will cause, annually, the loss of 10 million lives worldwide, in addition to an economic loss of 100 trillion dollars[2]. In the hospital context, the establishment of antimicrobial stewardship programs should be a priority[3]. The implementation of these programs in hospitals has resulted in improved clinical and safety outcomes, as well as a reduction in the use of antimicrobials, AR, and costs[4-8].

In order for the strategies adopted within the program to be successful, it is necessary to have a multidisciplinary team. Within this team is the clinical pharmacist, preferably with expertise in infectious diseases and the use of antimicrobials. The main activity of the pharmacist in this program involves auditing the prescription of antimicrobials, where the indication, dosage and duration of treatment are reviewed, contributing to the reduction of inappropriate use[9].

Although an antimicrobial stewardship program is already well established in the respective hospital, there are few studies demonstrating the implications of the strategies involved in the use of these medications. In view of this, this work proposes to evaluate the clinical significance and degree of importance, the acceptability rate and the minimized cost of strategies in the use of antimicrobials in a public teaching hospital, a reference in cardiopneumology in the state of Ceará from June to October 2023.

METHODS

This is a prospective study, with a descriptive and quantitative approach to the implications of the recommendations of a team of infectious disease physicians and clinical pharmacists from an Antimicrobial Management Program (AMP) of a public teaching hospital in Fortaleza, Ceará, from June 1 to October 31, 2023. The tertiary level hospital is a reference in cardiopulmonary, pediatric and adult treatment, with 463 inpatient beds. The present research was carried out in the units monitored by the PGA, which were the adult wards (B, C, H and J) and adult ICUs (Semi-intensive, Respiratory,

Cardiopulmonary, Coronary and Risk) and Pediatric and Post-Infant ICUs, totaling 251 beds.

Data were collected through the analysis of electronic medical records contained in the institution's hospital management system, IntegraSH and available in the PGA follow-up forms, made available by the Ceará State Health Department and the Ceará School of Public Health. Other instruments such as interviews and questionnaires were not necessary for data collection, since this is a research with secondary data.

The variables collected were number of patients followed, age, antimicrobials used, doses administered, routes of administration, length of hospital stay, duration of treatment, previous use of antimicrobials, clinical outcome, recommended strategies, and cost of treatment. These data were recorded in the PGA database, using Microsoft Excel® 2016 software. The descriptive analysis was conducted by calculating the means, absolute and relative frequencies of the variables.

For the research, antimicrobials classified as those in the therapeutic reserve group (which refer to those with the greatest spectrum of action) and in the strategic group (subject to conversion from intravenous (IV) to oral (OV) therapy) were considered.

Data on monotherapy treatment of antivirals, aminoglycoside antibiotics, macrolides and some of the beta-lactam antibiotics – penicillins and cephalosporins, which, in monotherapy, are not part of the follow-up by the program and are classified as "other" – were not included in the study. Topically applied antimicrobials are also not included due to the difficulty of measuring the amount used by the patient.

Regarding the recommended strategies, the following data were collected: type of strategy, classification of clinical significance, unit in which the recommendation was made, type of antimicrobial involved, and acceptability rate. The type of strategy is categorized according to the National Guideline of the Antimicrobial Stewardship Program9, as follows: dose adjustment; escalation or de-escalation; vancocinemia; oral sequential therapy (OST); *terapy switch*; *step down*; optimization of therapy; prolongation of treatment time; reduction of treatment time; end of treatment and other strategies such as requesting the opening of an antimicrobial form in the electronic medical record and requesting laboratory tests such as cultures.

The evaluation of the clinical significance of the recommendations was carried out based on a scale developed by *Spinwine* et al. (2006)[10], in an adapted manner, ranging from situations of extreme risk to minor risk. 1) Extreme: indicates that the recommendation avoided death or serious harm. 2) Major: the recommendation can prevent severe morbidity, including readmission, severe organ dysfunction, or severe Adverse Drug Event (ADE). 3) Moderate: recommendation that brings care to a more acceptable and appropriate level of practice or that can prevent a moderately important ADE. 4) Minor: no benefit or minor benefit.

In addition, the clinical significance of the recommendations was also classified into the following types: increasing treatment efficacy, reducing treatment toxicity, avoiding unnecessary antimicrobial exposure, and unknown significance.

To measure the acceptability rate of the recommendations, the relationship between the number of proposed strategies and the number of accepted strategies was considered.

The direct minimization of costs resulting from the strategies of dose adjustment, TSO, reduction of treatment time, *switch therapy* and de-escalation, called minimizing strategies, were performed according to the actual cost of acquisition between the previously prescribed therapy and the new therapy recommended by the PGA team. To calculate the cost reduction, we used the unit value of the pharmaceutical form of each antimicrobial and the number of units saved based on the treatment time actually performed. The information inherent to the acquisition value of the drugs was obtained from secondary data from the institutional information system ALMOX, linked to the IntegraSH electronic system.

The study project was approved by the Research Ethics Committee under consolidated opinion number 6,162,089.

RESULTS

From June to October 2023, 553 patients were followed, of which 93.67% (n= 518) were adults and 6.33% (n= 35) were pediatric. Of the adult patients, 51.16% (n= 265) were hospitalized in ward beds and 48.84% (n= 253) in ICU beds. The mean age of the 518 adult patients was 63.19 years, with 239 in the age group of 17 to 65 years, with a mean of 48.59 years, and 279 were over 65 years, with a mean of 75.70 years. The pediatric patients (n= 35; 100%) followed were hospitalized in ICUs, with ages ranging from 1 month of age to 15 years of age.

The mean length of stay of the 553 patients was 30.20 days, where the mean follow-up time by the program was 17.61 days and the mean time of treatment with antimicrobials was 18.2 days. Of these, 50.27% (n= 278) patients had previously used antimicrobials, 11.75% (n= 65) did not, and 37.97% (n= 210) had not been informed.

Regarding the clinical outcomes of the patients, the highest prevalence was of clinical cures, 29.11% (n= 161), followed by 26.58% (n= 147) deaths, 24.95% (n= 138) discharges, 14.47% (n= 80) intra-hospital transfers to units without follow-up, and 4.88% (n= 27) transfers to other hospitals.

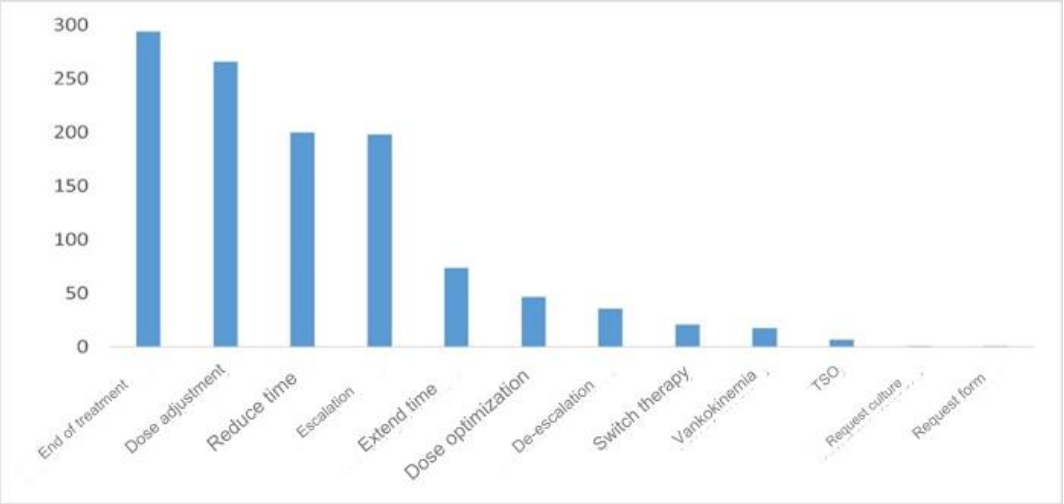
During the study period, 1659 antimicrobials were monitored, and 59.31% (n= 984) of them were recommended in some way. In 78.18% (n= 1,297) of the cases, culture was requested to support the prescription, of which 68.54% (n= 888) cases no pathogens were identified. Of the 409 cultures positive for a pathogen, in 81.90% (n= 335) cases the prescribed treatment was in agreement with the pathogen's susceptibility profile and in 18.09% (n= 74) cases it was in disagreement.

A total of 1165 recommendations were made, of which 64.55% (n= 752) were made in ICU patients and 35.45% (n= 413) in ward patients. The mean number of recommendations per patient was 2.27. Of these 1165 recommendations, only 5 were not accepted by the attending medical team, reflecting an acceptability rate of 99.57%.

The most common type of strategy in the present study was the completion of treatment according to institutional protocols with 25.24% (n= 294) of the recommendations, followed by dose adjustment with 22.83% (n= 266) of the recommendations, reduction of treatment time with 17.17% (n= 200) and escalation with 17.0% (n= 198) of the recommendations. The others included prolongation of treatment time (n= 74; 6.35%), dose optimization (n= 47; 4.03%), de-escalation (n= 36; 3.09%),

switch therapy (n= 21; 1.80%), vancocinemia (n= 18; 1.54%), oral sequential therapy (n= 7; 0.60%), *step down* (n= 2; 0.17%), request culture (n= 1; 0.09%) and request opening of an antimicrobial form (n= 1; 0.09%). Figure 1 illustrates all the recommendations made during the study period by type of strategy.

Figure 1. Number of recommendations by type of strategy in an antimicrobial stewardship program in a public hospital in Ceará.



Source: own authorship.

Avoiding unnecessary exposure to an antibiotic was the most common association of clinical significance of the recommendations, corresponding to 42.40% (n= 494) of the recommendations. Increasing treatment efficacy was implicated in 32.79% (n=382) of cases, while reducing treatment toxicity was implicated in 24.63% (n=287) recommendations. And 0.17% (n= 2) of the recommendations were not associated with any clinical significance, which were the situations of opening an antimicrobial form in the electronic medical record and requesting culture.

Most of the reported recommendations were classified as higher (n= 588; 50.47%), followed by moderate (n= 575; 49.36%). The remaining 0.17% (n= 2) recommendations were of lesser importance. One recommendation was reported to be extreme (i.e., avoided a potentially fatal error) during the study period.

Direct cost reduction was implicated in 45.84% (n= 534) of the accepted recommendations and was estimated at R$ 115,843.75. The strategy that produced the greatest impact on cost minimization was the dose adjustment, estimated at R$ 72,613.53, followed by the strategy to reduce treatment time, R$ 38,853.03, representing 62.68% and 33.54% of the total savings, respectively. Table 1 shows the total cost savings resulting from the accepted strategies.

Table 1. Cost minimization resulting from the recommendations of an antimicrobial management team in the months of June to October 2023.

Estimated financial cost	R$ 358.853,39
Realized financial cost (with strategies)	R$ 243.009,64
Financial impact	R$ 115.843,75

Source: own authorship.

DISCUSSION

As it is a hospital for the care of patients with heart disease and lung disease, who are mostly elderly, the number of patients in this age group followed by the PGA was consequently quite expressive. Of the 553 patients, 279 were over 65 years of age, divided proportionally among the wards and ICUs of the hospital. Generally, this finding is justified by the fact that elderly individuals are more susceptible to infections compared to young adults, due to physiological changes resulting from aging, decline in immune response and invasive procedures, requiring more frequent and intensive care, as well as hospitalization to treat their clinical conditions[11].

The mean length of hospital stay of the patients followed, 30.20 days, was much higher than the averages documented in other studies, which were generally shorter than 10 days[12-13]. The hospital that was the protagonist of this study mainly treats patients who undergo surgical procedures, including transplantation, which may require a longer rehabilitation time, and eventually expose patients to a higher risk of contracting infections.

The duration of antimicrobial therapy, 18.2 days, was longer than the 7 to 10 days normally performed for most infections[14]. However, most patients followed by PGA have infections that are more complex to manage, including endocarditis, mediastinitis, tuberculosis, empyema, among others. In addition, it is also important to consider that a large portion of the patients, 50.27%, in addition to all the factors associated with their clinical conditions, had previously used antimicrobials. This previous use may have contributed to the development of AR and hindered the choice and management of drug therapy, ultimately prolonging the time patients received treatment.

Of the total number of patients followed-up, 29.11% were clinically cured by infection and 24.95% were discharged from the hospital, resulting in a prevalence of 54.06% of positive outcomes, similar to that found by Gross et al. (2001)[4], where the cure rate was 64%. Another 26.58% of the patients died, representing a negative outcome, and the other 19.35% who had internal and external hospital transfers could not be determined. In this scenario, it is worth noting that in the period studied there was a high prevalence of prescription of empirical treatments, where the results of 68.54% of the cultures were negative. It is known that inadequate empirical therapies are associated with a higher mortality rate[15], but more research is needed to explain this finding.

On the other hand, of the prescribed treatments in which there were positive culture results, 81.90% were in accordance with the sensitivity profile of the identified pathogens. Research shows that directing treatments based on culture results leads to lower antibiotic consumption and shorter hospitalization time, in addition to contributing to the reduction of AR[15-16].

The distribution of recommendations in our survey revealed that 64.55% of all recorded recommendations were made in ICU patients. A few explanations have been suggested to justify this high rate. In this context, it is known that ICUs constitute the greatest demand for antibiotics within the hospital environment[17], and studies indicate that up to 60% of the antibiotics prescribed in these units are considered inadequate[18-19]. Thus, PGA becomes indispensable for the proper management of antimicrobial therapy in these units.

The most prevalent strategy in the present study was to complete the treatment according to institutional protocols, with 25.24% (n= 294) of the recommendations. Part of this is due to prospective audits with feedback, carried out weekly in the units, with meetings between a physician from the ICU team, an infectious disease physician from the hospital infection control service, and a clinical pharmacist.

The second most prevalent strategy was to adjust the dose of antimicrobials, with 22.83% (n= 266) of the recommendations. This strategy is predominantly conducted by clinical pharmacists, who perform the technical analysis of medical prescriptions on a daily basis and quickly identify inconsistencies in the prescribed doses[20]. Part of this result is also attributed to the need to adjust the dose of the drugs according to the renal function of the patients.

The third and fourth most common strategies were to reduce the treatment time and escalate the use of antimicrobials, with 17.17% and 17.0% of the recommendations, respectively. In the case of piperacillin/tazobactam, which is a reserve antibiotic at the institution, 12.79% (n= 38) of the recommendations included reducing treatment time and 29.63% (n= 88) escalating to a higher-spectrum antimicrobial. As this antimicrobial is widely involved in the development of AR, the evaluation of these data is important to guide the actions that can be developed by the PGA.

It is noteworthy that, in the period studied, the acceptance of the proposed recommendations by the medical team was remarkably high, 99.57%, which is higher than most of the previously reported rates, which, on average, vary between 50% and 70%[21-22].

The clinical value of the recommendations made was associated, in most cases, with avoiding unnecessary exposure to an antimicrobial agent (42.40%), mainly due to strategies aimed at reducing treatment time and completing treatment according to institutional protocols. The search for an increase in the efficacy of the treatment, which is expected in most cases, was associated with 32.79% of the recommendations. This improvement was mainly justified by the broadening or decreasing of the spectrum of antimicrobial treatment, i.e., escalation or de-escalation, respectively, and the optimization of the doses administered. On the other hand, prevention of toxicity was foreseen in 24.23% of the recommendations, mainly due to dose adjustments. The implications of this are a reduction in the number of adverse events, excessive or subtherapeutic doses of medications, reductions in the length of hospital stay and costs, and a decrease in AR[4-8].

Finally, about half of the recommendations, 50.47%, were classified as major, i.e., very important. This result, together with the others found, confirms the role of the PGA operational team in the safety of the use of antimicrobials in the hospital environment. In addition, a potentially fatal incident was avoided during the study period in which Polymyxin B was erroneously prescribed instead of Colistin (Polymyxin E) to a patient with urinary focus septic shock. Fortunately, the mistake was identified and corrected in time to prevent therapeutic failure and/or more severe consequences.

This study showed an overall decrease in the direct costs of antimicrobial therapy. Almost half (45.84%) of the recommendations made resulted in a direct decrease in treatment costs, resulting in total savings estimated at almost R$ 116,000.00 in just 5

months. This result denotes the significant financial impact generated by the PGA, which can be attributed to the recommendations made by the operational team and to a high rate of acceptance by physicians. Other studies on antimicrobial stewardship have also shown a positive impact on hospital budgets[5,8].

CONCLUSION

As confirmed by previous studies, the strategies adopted within an antimicrobial stewardship program have demonstrated possible positive outcomes, both from a financial and clinical point of view, related to antimicrobial management by a team of clinical pharmacists and infectious disease physicians.

Some limitations of the research can be attributed to the implementation of the PGA. Among these, the absence of important clinical information in the program's database can be highlighted. Examples of this are patient information such as gender, diagnosis, and comorbidities, as well as information about treatment (data from cultures with identified pathogen(s) and antimicrobial resistance profile).

In addition, the recommendations made by the team are not fully recorded in the program's database, thus not reflecting the determination of the real dimension of their clinical and financial impact.

Future research may be conducted to examine the possible long-term positive impacts of PGA on additional aspects such as microbial susceptibility profile, mortality rates, and incidence of infections.

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