Title: Antibiotic Stewardship Program's potential impacts on financial and clinical outcomes in a public hospital: a Real-World study

Abstract

Background: In times of antibiotic resistance, Antimicrobial Stewardship Programs (ASP) emerge as a strategy to improve clinical outcomes and hospital resource management.

Methods: The study was conducted on a single-center retrospective cohort of adult inpatients admitted to a public hospital in Brazil's capital and submitted to ASP from September 2018 to April 2019, aiming to assess the clinical and economic impact of following ASP instructions.

Results: The medical records of 449 patients were included. Mean age was 54.92 years, with a predominance of male sex 273 (60.93%), and 374 (83.48%) had comorbidities. Only 52.56% of the prescriptions followed the guidelines of ASP. The study demonstrated a significant improvement in clinical outcomes, such as a reduction of mortality ($p=0.01$), of hospital length of stay ($p<0.01$) and of ICU admissions ($p<0.01$). We also detected potential savings per patient provided by compliance with ASP's recommendations.

Conclusion: The present study was able to demonstrate positive clinical outcomes associated with the implementation of an ASP in a real-world scenario.

Extra information

1. **What is already known about this topic?**

   Antibiotic Stewardship Programs (ASP) were developed as a tool to prevent antimicrobial resistance. Nowadays, some studies have suggested that these programs can also improve clinical outcomes and financial savings. However, these topics are still controversial and haven't been largely studied in Low and Middle Income Countries.

2. **What does this article add?**

   The present research article contributes with a better understanding of ASPs' benefits in a real world scenario. Similar to other low and middle income countries (LMICs), financial challenges in the Brazilian public health system could be an obstacle to health care. The stewardship program can play an important role in overcoming this matter by saving costs related to hospitalization, without compromising patient care.

Keywords: Anti-Bacterial Agents; Antimicrobial Stewardship; Drug Prescriptions; Bacterial infection; Mortality.

INTRODUCTION

Since their discovery, antimicrobials have served as a cornerstone of modern medicine, evolving and becoming a hallmark in the combat against infectious diseases.[1] However, the persistent overuse and misuse of this type of medication ended up by triggering the emergence and spread of antimicrobial resistance (AMR), which jeopardizes the ability to respond effectively to infectious diseases and affects the provision of preventive and curative healthcare.[2]

Infections by multidrug resistant bacteria (MDR) can lead to worse clinical outcomes, such as elevated mortality rates, higher morbidity and increased length of hospital stay. Also, AMR can translate into greater resource expenditures, elevating healthcare costs.[3,4] The growing concern raised by the increase in AMR has led the World Health Organization and other healthcare institutions to promote stronger antimicrobial management programs.[1,5]

The term *antimicrobial stewardship program (ASP)* refers to an interdisciplinary approach to the selection of the optimal drug, dosage and duration of therapy aiming at the best clinical outcomes, with decreased toxicity and the prevention of bacterial resistance.[6]

A Cochrane review defined three types of ASPs according to their intervention methods. Persuasive interventions are based on educational programmes, audits and feedback. Restrictive methods may use forms as tools for requiring prior authorizations of prescriptions by infectologists, microbiologists or pharmacists. The third type of ASP is called “structural”, since it depends on computerized records to provide rapid diagnostic and decision support systems for antibiotic prescription.[5]

An additional goal of ASP is to reduce healthcare costs – i.e. expenditures regarding drug consumption, hospitalization and treatment of adverse effects - without adversely impacting patient safety.[4,6]

Studies conducted in other countries were conflicting regarding not only the financial impact of ASP, but also its impact on clinical outcomes.[7,8,9] These programs have only recently been discussed in Brazil and are still being implemented in some regions of the country. Most of the existing studies have been conducted in intensive care units (ICU), while wards are less studied settings.

The aim of the present study was to evaluate the impacts of a stewardship strategy on clinical outcomes, also assessing the repercussions of ASP from the perspective of potential economic savings outside the ICU.

METHODS

Study design and setting

The study was conducted on a single-center retrospective cohort included in the ASP of a public hospital in Brasilia, Brazil's capital. This hospital is an 833 bed tertiary-care teaching facility with both clinical and surgical wards. It is considered a reference center for the region since it supports not only the city's own population but also patients referred from primary and secondary healthcare units from surrounding cities.

ASP implementation

The Hospital's Infection Control Commission was responsible for the development of the ASP. Since its implementation in 2018, attending doctors are required to fill out a notification form in order to prescribe the antimicrobials listed in Table 1. This document contains information regarding site of infection, prescribed drug, length of treatment, route of administration, dosage, risk factors for MDR (hospitalization within the last 90 days, immunosuppression, use of broad spectrum antimicrobials within the last 90 days, and previous colonization with MDR) and other information detailed in Additional file 1. The prescriptions are then analyzed by the ASP in order to meet better practice for antimicrobial therapy according to the hospital's standard operational procedures. The suggestions can be either verbally discussed with the attending doctors or communicated through the patient's electronic medical record network.

Due to the limited economic resources of the Brazilian public health system, the ASP was implemented on a gradual basis, initially as a consulting group consisting of infectious disease physicians and a clinical pharmacist working on the hospital's wards. During the period that preceded this study the audit did not have a restrictive nature, allowing the clinical staff to decide whether or not to follow the provided recommendations. This scenario led to a unique opportunity to assess the impact of compliance with ASP recommendations on patient outcome and treatment costs, permitting to obtain Real-World Evidence (RWE) from homogeneous comparison groups. The included patients were divided into compliant and non-compliant groups according to the decision of the attending physician.

Study design, population and data sources

This research included prescriptions for patients admitted to the hospital wards and analyzed by the ASP from September 2018 to April 2019. The information was collected from an electronic medical records network (Trakcare by InterSystems), from prescription files and from the ASP database. Patient data were analyzed by seven medical students, double-checked by a different reviewer, and assessed by an attending doctor.

The following data were collected from each prescription included: patient general data, clinical and laboratory parameters on the first day of antibiotic use, Glasgow Coma Scale, hemodynamic stability, peripheral O_2 saturation and fraction of inspired oxygen, creatinine, liver enzymes, bilirubin levels, hemoglobin, leukocytes, and platelet count. The outcomes analyzed were mortality, total length of hospital stay and days of hospitalization after the prescription, need of ICU, antimicrobial therapy escalation, most common adverse drug reactions, and costs related to hospitalization and therapy.

Exclusion criteria were: age < 12 or > 90 years prior to admission to the ICU or need for mechanical ventilation before antibiotic prescription, refractory shock or reversed cardiopulmonary arrest before admission, lack of information in medical records, single antibiotic dose use, advanced comorbidities or request for limited invasive care. We considered advanced comorbidities to be: chronic liver disease (CHILD-PUGH C), previous stroke resulting in severe limitation of self-care, advanced dementia, metastatic cancer without treatment perspective, chronic renal failure requiring dialysis, congestive cardiac failure with an ejection fraction < 30%, and chronic lung disease in need of continuous oxygen therapy.

Cost analysis

The major parameters evaluated in order to analyze the potential financial savings with ASP implementation were hospitalization and antimicrobial prescription-related costs. The average cost was calculated for each patient.

The hospitalization costs considered during the patient's stay were water and meal consumption, procedures, medical material, and human resources. Since these variables may vary according to each hospital department, an average cost was provided by the hospital's financial sector. The hospitalization cost per day was estimated at R$ 969,96 (US$ 245,89/€ 219,56).

Antimicrobial expenditure was estimated with the standardized tool of Defined Daily Doses (DDD) recommended by the WHO in 2020, considering the chosen drugs and therapy length. When a given antimicrobial did not have a recommended DDD by the WHO, a typical dose for an adult male without hepatic or renal comorbidities was considered.

Next, we estimated the difference between the compliant and noncompliant groups and assessed the potential reduction in expenses obtained with ASP implementation. The cost of ASP itself was not calculated because the program had not been fully implemented when this study was carried out.

Values were collected and analyzed using the local currency (Brazilian Reais R$), and then converted to dollars considering the April 30, 2019 exchange rate provided by the Brazilian Central Bank website.

Statistical analysis

The Google Sheets platform and Microsoft Excel were used for data tabulation and data were analyzed statistically using Microsoft Excel and GraphPad Prism 8 for Windows.

Nominal variables were summarized as frequency counts and percentages, continuous variables were summarized as mean and standard deviation, and discrete and ordinal variables as medians and IQR 25-75%. Comparisons were made between two groups of prescriptions categorized based on whether ASP recommendations were followed or not. Differences in normally distributed continuous variables were analyzed by the Student T Test while differences related to ordinal and discrete variables were determined by non-parametric tests. Dichotomous variables were assessed by Fisher's Exact Test and/or Chi-Square test.

For side effects, major complications, ICU admissions and death we calculated Relative Risk (RR), Confidence Interval (CI) and Number Needed to Treat (NNT).

All tests were two-sided and conducted at the 0.05 level of significance; their statistical power was calculated with the G*Power 3.1.9.7 software and was considered if greater than 0.8.

Ethics and reporting

Since the research involved human beings, evaluation and approval by the Hospital Ethics Committee was requested and granted. Informed consent was not required since this was a retrospective, observational and anonymous study.

RESULTS

A total of 913 medical records were analyzed, 449 of which were included and 464 excluded. Among the 464 prescriptions excluded, 294 (63.36%) belonged to critical patients (prior admission to the ICU with length of stay of more than 48 hours or need of mechanical ventilation, exclusive palliative care or death within 24 hours of admission), 133 (28.66%) were excluded due to lack of data, 28 (6.03%) used a single dose of antimicrobial medication, and 9 (1.95%) were in extreme age ranges (under 12 or over 90).

Mean patient age was 54.92 years, with a predominance of male sex, 273 (60.93%), and 374 (83.48%) subjects had comorbidities. Overall sample mortality was 14.2% and average length of hospital stay was 30.44 days. A prevalence of 49.89% was found for community-acquired infections, 36.81% for nosocomial ones and in 13.30% of cases these data were not available. The most prevalent sites of infection were respiratory system (23.78%), soft tissues (10.89%) , urinary tract (16.89%), and abdominal cavity (14.89%). The most prescribed antimicrobials were Piperacillin/Tazobactam (19.51%), Ciprofloxacin (13.30%), Ceftriaxone (11.31%), Meropenem (9.76%), Vancomycin (8.20%), Cefepime (7.98%), and Ampicillin/Sulbactam (5.32%).

Among the corrections analyzed, the most prevalent one was length of antibiotic therapy (79.38%), followed by antibiotic doses (10.89%) and interval between doses (9.73%). A new antibiotic scheme was suggested by ASP if the program judged that the initially prescribed one was not adequate for the patient, a situation that occurred in 3.1% of the sample. The changed suggestions were registered in the patient's electronic medical record in approximately one third of the cases.

The medical records were further divided into two groups, compliant (236 prescriptions) and noncompliant (213 prescriptions), according to their compliance with the institutional protocols and Antimicrobial Stewardship recommendations. The general characteristics of each group are detailed in Table 2, while the main outcomes are described in Table 3.

In order to minimize the confounding factors, we assessed patient severity by calculating the SOFA score, which is related to sepsis prognosis[10], on the first day of antimicrobial prescription. The score did not differ significantly between the compliant and noncompliant groups.

The average cost of hospitalization and antimicrobial prescription for each group is presented in Table 3. The estimated general hospitalization costs were 1.58 times higher for the noncompliant group ($p < 0.01$). Regarding antimicrobial expenditure, the average cost per patient was estimated as R$ 2.877,43 (US$ 728,88; € 651,34) for the noncompliant group and as R$ 1.449,63 (US$ 367,20; € 328,14), (p = 0.57) for the compliant group. Comparison of the estimated average cost difference between the compliant and noncompliant group revealed a potential saving of R$ 11.114,84 (US$ 2816,022; € 2515,97) per patient in the compliant group.

When the NNT of ASP compliance was calculated for death, a value of 12 was obtained. Similarly, the NNT to avoid one ICU admission was 8. To prevent side effects such as nephrotoxicity, hepatotoxicity and hypersensitivity, the NNT was 15. Finally, 8 compliant prescriptions were needed to prevent a major complication such as antimicrobial escalation (Table 4).

DISCUSSION

Assessment of the quality of antimicrobial prescription should be the first step in identifying the target for further improvements. To this end, many variables must be taken into consideration, such as: microbiological data, the correct drug choice (according to local resistance patterns), dosage, therapy duration, and route of administration. A second step is to ensure that ASP recommendations are incorporated into clinical practice for an effective positive impact on patients. [11]

In an attempt to validate the current status of ASP as a mechanism to enhance health care assistance in a low-and-middle income country, our compliance rate in a real-world scenario proved to be suboptimal, since the corrections performed by the ASP were followed in only approximately half the cases. Higher rates of 64.1%[12] and even 80%[13] were reported by Magedanz et. al. and Pate et al., respectively.

Bio et. al. and Duane et. al. identified predictive factors for noncompliance with ASP recommendations that were also present in our study, such as intra-abdominal or soft tissue infections, corrections directed at surgical units and suggestions to reduce or suspend medications. Other factors such as more years of attending experience of the prescribing doctor have been described. García-San Miguel L et al reported that higher compliance rates were found when written recommendations were used along with verbal guidance. In the present study, the electronic medical record was used for this matter in only one third of the corrections.[14,15,16]

The main correction indicated by our ASP was therapy length, resulting in a reduction of about 10 days of hospital length of stay (LoS) for the compliant group. Cosgrove et al. stated that a longer hospital stay and use of antimicrobials are related to medical resistance to interrupt therapy, even if there is no evidence of bacterial infection[17]. The current literature still finds the impact of ASPs on decreasing LoS to be controversial. Camins et al. conducted a randomized controlled trial to assess this matter and also attested a decrease in LoS. Karanika et al. and Brahmi et. al. reported similar findings, while Cabrera et al. and Standiford et al. reported no difference in this outcome.[18,19,20,21,22.]

According to Kollef et al, inadequate antimicrobial treatment is associated with increased mortality in infected patients.[23] Regarding the implementation of ASPs, changes in mortality rates can help ensure the program’s safe implementation by warning if mortality increases and can also provide information about the program's positive impacts if a reduction in these rates occurs. Therefore, mortality was the main clinical outcome evaluated in our study.

Ng et al. conducted a retrospective analysis comparing the 1-year pre-ASP period to the 1-year post-ASP period in a 1800-bed regional hospital and found no difference in overall mortality or infection-related mortality rates. Similarly, Standiford et al. reported no significant changes in this parameter in a 7 year program at a large tertiary hospital.[22,24] Two randomized prospective studies also did not demonstrate improvements in in-hospital mortality rates[19,25], in agreement with a meta-analysis performed by Karanika et al. that found no impact of ASP on this endpoint.[18] Slightly different results were obtained by Chan et al.,[26] who found a modest decrease in infection-related death rates during the years that followed the implementation of an antibiotic restriction program. These rates, however, are susceptible to important confounding factors that most likely did not affect our sample, such as possible changes in medical team and in patient population over the years.

Our cohort, in contrast, showed an expressive decrease in mortality in the compliant group. Honda et al., in a recent meta-analysis, reported that studies that assessed mortality in before-and-after trials – such as the ones mentioned above - could not demonstrate a significant impact on this outcome. On the other hand, studies with a design similar to ours - two comparative groups, with the ASP as the only difference between them - found a substantial reduction in death rates.[8]

Other studies have used different tools to improve the practice of prescribing antimicrobials, also finding reductions in mortality rates[27,28]. Although the interventions evaluated in these studies were not formal ASPs, they included formal guidance and sought to improve attention about the prescription of antimicrobials, as done by the ASPs.

In our population, compliance with ASP recommendations caused an almost two-fold reduction of the incidence of adverse drug reactions (ADR) observed during the period of antimicrobial use (7.63% vs. 14.08%, p = 0.032), indicating the potential of the Stewardship to reduce this kind of damage. Tamma and colleagues conducted a retrospective cohort study with adult patients receiving systemic antibiotic therapy while hospitalized on general medicine wards. They detected a 20% incidence of ADR, with a 10% increased risk for these events every 10 additional days of antimicrobial therapy, using a longer follow-up time than ours, i.e., 30 days from the first day of antimicrobial prescription for the most common adverse effects and 90 days when dealing with Clostridium difficile infection and the development of multidrug-resistant organisms.[29]

A recent study by Kokado et al. reported a 22.3% rate of antibiotic-associated adverse drug reactions.[30] The non-compliant group's ADR rate was consistent with these studies. Since compliance with ASP recommendations was the only distinction between our groups, it is reasonable to assume that adherence reduces the incidence of ADR.

A previous study on a computerized decision-support program found a reduction in ADR (4 vs. 18, $p < 0.02$), a result closely similar to ours.[31] Other stewardship studies have been limited to the evaluation of single antimicrobial ADR[32,33]

Few studies have assessed the impact of ASP on other complications such as need for ICU or antibiotic escalation. In the single-center study conducted by Ng et.al. that analyzed outcomes 1 year before and 1 year after the implementation of an ASP, no significant differences were described regarding the need for intensive care.[24] On the other hand, our results showed that patients who had their prescription adjusted not only needed less ICU admissions but also had lower rates of antimicrobial escalation.

Concerning cost evaluations, multiple studies have mentioned the difficulty imposed by various approaches and the lack of a defined calculation method. A recent literature review also revealed that few studies had economic analysis as the primary objective.[34,35]

Our study demonstrated a significant potential saving per patient as a result of compliance with ASP recommendations. A recent systematic review by Nathwani et al. pointed out that the average saving per patient was $732, while we found an average potential saving per patient of the compliant group of $1116,50. It is worth mentioning that most of the studies included in the review were performed in medium-sized hospitals. Furthermore, the cost of ASP implementation is potentially outweighed by the subsequent cost-savings.[9]

The results obtained also indicate an important saving regarding antimicrobial expenditure. A 50.10% reduction in costs was detected when comparing the compliant and non-compliant groups, which is above the average reported in similar studies[9]. Ruttimann et al. and Cabrera et al. evaluated ASPs that included educational aspects and case discussions, reaching similar results: 56% and 55%, respectively.[21,36] Other studies have also reported a reduction in total expenditures after the implementation of ASP, with the greatest impacts being associated with antimicrobial prescriptions.[22]

Finally, few studies have assessed the impact of ASP on operational costs, i.e, costs related to length of stay, diagnostic procedures and treatment.[9] The compliant group showed a significant decrease in hospitalization costs compared to the non-compliant group. Likewise, the current literature points to a patient's reduced length of stay following ASP implementation, which indirectly leads to a decrease in operational costs.[9,37] Although our saving results are superior to most of those reported in the available studies, this is mainly a reflection of the great improvement in the clinical outcomes of inpatients. In addition, the noncompliant group indicated that our ASP could be potentially enhanced, improving clinical results and savings and also contributing to the refinement of prescriptions. According to the framework proposed by Nathwani et al., the ASP could work as a central point between better clinical outcomes and the reduction of antimicrobial use, resulting in higher value for the healthcare system[9]. However, the savings obtained with the program's implementation tend to decrease along the years as the prescriptions profile improves, favored by the educational actions of ASP.[38]

At a time when antimicrobial resistance is a global public health crisis, low- and middle-income countries face a disproportionate burden related to this matter, not to mention the challenges related to resource availability.[39] Van Dijck et. al. performed a systematic review aiming to evaluate the impacts of ASP in such countries, but reported low study quality and heterogeneity of interventions and outcomes.[40]

Our study, conducted in a unique real-word scenario thanks to such circumstances, permitted a stepwise approach to the establishment of an ASP while acknowledging the particularities of a developing country. This method allowed a retrospective comparison between two contemporary groups with similar characteristics that were submitted to similar hospital care, differing only by compliance or not with the guidelines provided. This particular scenario ensured greater comparative strength, enhancing the study's findings.

Limitations

Our study had some limitations. Although the data obtained were submitted to a review process and compared between different information sources within the digital medical record system (i.e. antimicrobial prescription records, medical records and ASP database), they were still susceptible to filling errors and missing information. The savings were only estimated because we used an average cost per patient and we were unable to measure the costs of implementing the ASP in order to calculate the cost-effectiveness of the program. Since we used DDD to estimate the antibiotic costs, we did not evaluate the savings related to the reduction in the daily dose of some prescriptions; thus, the potential savings found in this study may have been underestimated. Furthermore, the reasons for low compliance are multifactorial and could not be totally evaluated in our study.

Also, this study was conducted at a public hospital within a low-and-middle income country and its results cannot be generalized to different realities.

CONCLUSIONS

In summary, the present study was able demonstrated positive clinical outcomes associated with the implementation of an ASP in a real-world scenario: average length of hospital stay, need for ICU, need for antibiotic escalation, adverse drug reactions, and mortality rates were significantly lower among the compliant group.

Our study also explored the potential economic impacts of compliance with the program's recommendations and detected great potential savings. Moreover, similar healthcare centers belonging to the Brazilian public health system can find in ASP a useful tool for achieving the mentioned goals. More studies in comparable and different scenarios are necessary to provide a better understanding of the repercussions of such programs.

The positive impacts of our study were not greater due to low compliance rates. Thus, new strategies are needed to increase the prescribers' adherence to the Stewardship program, with further studies assessing the reasons for such low rates and evaluating possible interventions.

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Table 1 Antibiotics that require filling out notification

Antifungals	Amphotericin B
Penicillin	Piperacillin-Tazobactam, Ampicillin/Sulbactam
Cephalosporin	Ceftriaxone, Cefepime, Cefazolin
Carbapenems	Ertapenem, Meropenem
Quinolones	Ciprofloxacin, Levofloxacin
Glycopeptides	Teicoplanin, Vancomycin
Lipopeptides	Daptomycin
Oxazolidinones	Linezolid
Glycylcyclines	Tigecycline
Polymyxins	Polymyxin B
Lincosamides	Clindamycin
Aminoglycoside	Gentamicin, Amikacin
Macrolide	Azithromycin

Nitroimidazoles	Metronidazole

Table 2 General Characteristics of the study Groups

	All patients (449)	**Compliant patients (236)**	**Noncompliant patients (213)**	**p value**
Age (mean/SD)	54.92 (18.77)	53.49 (19.38)	54.92 (18.67)	0.30
Male sex (%)	60.93	59.75	61.50	0.59
Comorbidities[1] (%)	83.48	83.05	86.28	0.13
Risk Factor for MDR[2] (%)	65.56	60.63	68.58	0.22
Hemoglobin (median/IQR 25-75)	10.9 (9.0-12.7)	11.3 (9.0-13.1)	10.6 (8.9-12-7)	0.09
Leukocytes x 10^3 (median/IQR 25-75)	10.9 (6.8-15.1)	9.5 (5.4-14.9)	10.5 (6.8-14.9)	0.04
Platelets x 10^3 (median/IQR 25-75)	234 (150-345)	211 (132-328)	245 (162-369)	0.00
Creatinine (median/IQR 25-75)	1.0 (0.8-1.6)	0.9 (0.8-1.3)	1.0 (0.8-1.5)	0.73
Bilirubin (median/IQR 25-75)	0.5 (0.3-0.9)	0.5 (0.4-0.8)	0.6 (0.4-1.0)	0.84
SOFA score (median/IQR 25-75)	3 (0-4)	3 (1-4)	2 (0-5)	0.70

[1] Hypertension, diabetes, oncological, cardiological and neurological affections, pulmonary, hepatic, nutritional, renal and rheumatological comorbidities.

[2] Hospitalization or use of broad spectrum antibiotics within the last 90 days, previous colonization with MDR, immunosuppression.

Table 3 Outcomes

	Compliant patients (236)	Noncompliant patients (213)	p value
Antimicrobial duration	11.2 (4.4)	16.1 (9.5)	<0.01
Hospital stay	25.1 (27.1)	36.3 (31.2)	<0.01
Adverse Drug Reactions	7.63	14.08	0.03
Antimicrobial escalation	18.30	31.34	<0.01
ICU Admissions	13.79	25.71	<0.01
Death	10.17	18.78	0.01
Estimated antimicrobial costs per patient	R$ 1449,63	R$2877,43	0.57
Estimated general hospitalization costs per patient	R$ 16.584,00	R$ 26.271,00	< 0.01

Table 4 Increased risk of poor outcome in the noncompliant group

	Relative Risk (RR)	Confidence interval (CI)
Side Effects	1.847	1.070 to 3.198
Major Complications[1]	1.712	1.218 to 2.417
ICU Admission	1.864	1.261 to 2.768

Death	1.106	1.025 to 1.201

[1] Complications that required a change of antimicrobial medication.