Clinical and economic impact of the implementation of an antimicrobial stewardship program in four Colombian healthcare institutions

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Abstract

Background Despite multiple reports of the benefits of antimicrobial stewardship programs (ASPs) in developed countries, regarding patient safety, decrease in antimicrobial resistance, consumption and spending on antimicrobials, there is very limited evidence of the same benefits in a different economic and social context. The objective of this study was to evaluate the clinical and economic impact of the implementation of an ASP in Colombia. **Methods** We conducted a multicenter, quasi-experimental cohort study in four Colombian healthcare institutions between 2007 and 2014 including 900 patients (429 patients before and 471 after the implementation of the ASP) to evaluate the impact of these programs. **Results** Compared to the pre-ASP, the post-ASP group showed a greater adherence to the use of the empirical therapy and de-escalation based on the guidelines (45% vs. 9% and 92% vs. 8%, respectively; $p < 0.001$), as well as a higher proportion of clinical cure at the end of treatment and lower mortality (93% vs. 74% and 14% vs. 28%, respectively; $p < 0.001$). In the post-ASP patient group the opportunity for clinical improvement was 10 times greater compared with the pre-ASP group (adjusted OR = 10.40 95% CI 1.21-89.41) and there were less complications following targeted management (adjusted OR = 0.49 95% CI 0.25-0.97). Furthermore, after the implementation of the ASP there was lower average expenditure associated with hospital stay, laboratory tests, infectious diseases consultation, and empirical antimicrobial therapy choice. **Conclusion** With this study, we were able to show that even in limited income countries, ASPs are feasible to implement.

Background

A growing body of evidence demonstrates that strategies dedicated to promote the rational and effective use of antimicrobial agents including antimicrobial selection, dosage, route of administration and duration of therapy, commonly referred to as antimicrobial stewardship programs (ASPs), are a key component to address antimicrobial resistance in hospital and ambulatory healthcare settings and even in agriculture (1,2). Besides, ASPs have been shown to improve patient care by enhancing optimal therapy with lower rates of treatment failure and reducing collateral damage associated with antimicrobial administration, intravenous lines and length of hospital stay. Moreover, these programs often achieve these benefits while saving hospitals money (3).

In Latin America, many countries are in the process of developing ASPs. However, although the effectiveness of these strategies is proven in North-American and European countries to have a positive impact on patient care, antimicrobial resistance and healthcare economics (4,5), there is very few literature on the impact of ASPs in developing countries in general and even less in Latin American countries (6). In addition, these studies mainly focus on the impact of ASPs on antimicrobial consumption and resistance. This situation is concerning since healthcare systems in developing countries count with very limited resources, meanwhile antimicrobial resistance rates usually are higher compared to developed countries (6–8).

Therefore, the objective of the current study was to determine the clinical and economic impact of the implementation of an ASP in four Colombian healthcare institutions in patients with community- and healthcare-acquired infections.

Methods

A multicenter, quasi-experimental, retrospective cohort study was conducted between January 2007 and December 2014 comparing clinical and economic outcomes in patients with community-acquired infections (CAIs) and healthcare-acquired infections (HAIs) before and after the implementation of an ASP (Figure 1).

Implementation and structure of the ASP

The implementation process took between 6 and 12 months and was executed individually in each of the four institutions. All hospital ASPs had several characteristics in common: (A) the multidisciplinary antimicrobial stewardship (AMS) team was led by an infectious disease specialist; (B) all participating institutions had previously established antimicrobial guidelines; (C) infectious disease specialists, epidemiologists, pharmacists, microbiologists and general practitioners were part of the multidisciplinary team; (D) new guidelines for the most prevalent infectious diseases were elaborated based on the local microbiology or existing guidelines were updated by the ASP team and specialists of different clinical areas; (E) antimicrobial guidelines were socialized with all healthcare professionals; (F) active antimicrobial prescription surveillance with constant feedback regarding appropriateness (according to institutional guidelines) towards prescribers was performed by a general practitioner in three out of the four hospitals, in contrast with only one institution that implemented restrictive prescription control; (G) educational activities were implemented in every participating institution according to their needs.

Study population

We included patients aged 18 years and older with CAIs and HAIs, from four tertiary care institutions in two Colombian cities (Cali and Barranquilla) (Table 1). We excluded patients receiving only peri-operative surgical prophylaxis, those with fungal infections, those whose care was limited to the emergency department, those with infections not included in the institutional antimicrobial guidelines, and those with incomplete clinical records. Inclusion and exclusion criteria were applied retrospectively.

Sample size was estimated for the outcome of “adherence to antimicrobial guidelines” based on a confidence level of 95% and statistical power of 80%, assuming an adherence of 70-90% among participating institutions and a 10% adjustment for non-response.

Clinical outcomes

We collected information that included sociodemographic data, patient location in the hospital, diagnosis of infection, comorbidities, antimicrobial therapy during patient care, and complications during the hospital stay. Treatment prescribed during the first 24 hours of hospitalization was considered to be the

initial treatment and was recorded whether or not adhering to guidelines. Regarding clinical outcomes definitions, adequate empirical dose was defined as the administration of the antimicrobial dose established by the institutional guidelines; adherence to antimicrobial guidelines was defined as the accordance between the antibiotics chosen by the attending physician (for the diagnosed infection) and the recommendations included in the institutional guidelines (9); adequate de-escalation was defined as adjusting initial, adequate broad-spectrum treatment by changing the antimicrobial agent or discontinuing an antimicrobial combination according to the patient's culture results (10). Mortality was defined as death in the first 30 days following hospital admission.

The primary outcome was clinical improvement at 72 hours of empirical treatment, as well as clinical improvement at 72 hours of targeted treatment. Clinical improvement was defined as the resolution of the systemic inflammatory response after three days of empirical treatment or guided by antibiogram. Clinical cure at the end of treatment was defined as the resolution of all the signs and symptoms of the infection at the end of antibiotic treatment. For systemic inflammatory response syndrome (SIRS), sepsis and septic shock, the definitions of the 2001 SCMM/ESCIM/ACCP/ATS/SIS International Sepsis Definitions Conference were applied (11).

Economic measures

The cost of care for patients with infections that were selected for the study corresponded to the sum of the infectious diseases consultations, antibiotic consumption, clinical laboratory tests, microbiological cultures and the length of hospital stay per patient. A partial economic assessment was carried out using micro-costing techniques as a way of determining the magnitude of the resources spent. The allocation of costs for each resource is based on a reference cost and is adjusted by inflation rate based on the Colombian manual document for costs (SOAT 2017 Tariff Manual).

Statistical analyses

Chi-square test or Fisher exact test were used to compare proportions between the two groups. Non-parametric statistics were calculated depending on the normality of the distribution. For the bivariate analysis, the odds ratio (OR) with 95% confidence interval (95% CI) was established independently for each variable of interest. In the multivariable analysis, logistic regression was carried out with the variables that presented a p value < 0.20 in the bivariate analysis. All p values < 0.05 were considered statistically significant.

This research was classified as minimal risk and the study was approved by the ethics committees of the participating institutions and the Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM) ethics and research committee.

Results

We included 900 patients with bacterial infections who were hospitalized in the participating institutions, including 471 exposed patients (post-implementation of the ASP) and 429 non-exposed patients (pre-implementation of the ASP) (Table 2).

Clinical outcomes of the ASP

The median age of included patients was 62 years and 54% of the patients were males. Before hospital admission, 52% were admitted from the community and 48% from other hospital or healthcare institutions; 70% of the patients had at least one comorbidity. Urinary tract infections were the most common infections among all patients (28%), followed by bloodstream infections (26%).

Statistically significant differences were present between pre- and post-ASP groups regarding comorbidities, previous history of surgery after admission, sepsis and septic shock at the time of infection (Table 2 and Table 3). Compared to the pre-ASP, the post-ASP group showed a greater adherence to the use of the empirical therapy and de-escalation based on the guidelines (45% vs. 9% and 92% vs. 8%, respectively; $p < 0.001$), as well as a higher proportion of clinical cure at the end of treatment and lower mortality (93% vs. 74% and 14% vs. 28%, respectively; $p < 0.001$). In the post-ASP patient group, the opportunity for clinical improvement was 10 times greater compared with the pre-ASP group (adjusted OR = 10.40 95% CI 1.21-89.41) and there were less complications following targeted management (adjusted OR = 0.49 95% CI 0.25-0.97) (Table 4 and Table 5).

Economic outcomes for the ASP

The expenditure on healthcare for infected patients not included in the ASP was higher compared to the patients who were included in the ASP (4,156 USD vs 2,952 USD, $p < 0.001$) (Table 6). When each item was individually analyzed and entered in the statistical analysis, there was significantly higher average expenditure related to hospital stay, laboratory tests, infectious diseases consultation, and empirical antimicrobial therapy choice in the patients not included in the ASP ($p < 0.001$). On the other hand, there was no statistically significant difference with regard to the targeted antimicrobial therapy choice. The monthly average cost for each of the ASPs was 3,785 USD (ranging between 2,469 and 5,488 USD).

Discussion

Despite the well acceptance of ASPs as a routine measure of quality improvement, these programs consist of a bundle of interventions, making it difficult to assess the impact of a single intervention and therefore a clear consensus is lacking (12). Outcome assessment in the pre- and post-ASP implementation periods becomes the most commonly employed study design, despite all its limitations, to mention, the retrospective nature and the quasi-experimental design of the study (13).

We consider that there are several elements that might have contributed to the observed outcomes. First, all four hospitals had antimicrobial guidelines based on their epidemiology elaborated by an infectious disease physician in conjunction with other relevant specialists. Inclusion of a multidisciplinary group to

approve and adopt the antimicrobial guidelines likely increased its adherence, as it is suggested by other studies (14). Second, all hospitals had a steward dedicated to the ASP at least part time. This person was previously trained in AMS concepts and strategies, hospital epidemiology, mechanisms of resistance in gram-negative and gram-positive bacteria present in each hospital, and when de-escalation was an option. Third, the steward was supported by the on-service infectious disease physician, the infection prevention and control committee, and the general manager of the hospital for any discrepancies in the therapeutic decision-making between the steward and the primary doctor in charge of the patient. These discussions frequently favored the steward recommendation to change the antibiotic (empirical, therapeutic or de-escalation). The adherence to de-escalation in the post-ASP period was greater (92%) compared to the pre-ASP period, which was only 8%. This suggests a very high credibility achieved by the ASP. Fourth, all but one hospital implemented prospective audit and feedback which, although is more time-consuming compared to the antibiotic pre-authorization strategy, generally is more accepted, resulting in higher clinical benefits such as less complications after the empirical antibiotic was started and greater proportion of adequate dosing (15).

Patients under the ASP in our study had a 14% reduction in mortality compared with patients prior to ASP implementation. A significant clinical improvement was achieved after ASP implementation, even though in the post-ASP period patients had statistically significant more neurological comorbidities, and an increased likelihood of sepsis at the moment of infection. There were no differences between the pre- and post-ASP groups regarding age and type of infection. The other benefit shown in the post-ASP was length of stay, which decreased 4 days in average. Our results are similar to a publication from 2013, which demonstrated that non-adherence to hospital antibiotic guidelines in a public hospital in Colombia, was an independent risk factor for mortality from HAIs (16).

Finally, our study suggests an economic benefit associated with the ASP in each hospital. The average expenditure associated with hospital stay, laboratory tests, infectious diseases consultation, and empirical antimicrobial therapy choice was higher for patients in the pre-ASP period. Our study did not evaluate other costs not directly related to infections. Nevertheless, some studies suggest that ASPs are able to reduce non-infectious disease expenditures related with adverse events or complications during hospital stay (17).

Our results are in line with what was previously described by Dik et al (1), who showed that ASPs in a short term are able to improve patient care by increasing adherence to optimal antimicrobial therapy and, in a short to intermediate term, reduce collateral damage. These effects are due to a lower exposure to antimicrobial toxicity, fewer *Clostridioides difficile* infections, reduced number of catheter-associated infections due to shorter intravenous treatment regimens, and less non-infectious complications associated with shorter hospital stay as described previously. In an intermediate to long term, ASP benefits are usually the reduction of antimicrobial prescription as well as bacterial resistance. All previously described factors contribute to a reduction of hospital costs.

Conclusions

This study comparing a pre- versus a post-ASP implementation period in four Colombian hospitals was able to show the feasibility of implementing ASPs along with optimization of healthcare expenditures, confirming that ASPs may have a great impact for Latin American countries and other resource-limited countries.

List Of Abbreviations

AMS: Antimicrobial Stewardship

ASP: Antimicrobial Stewardship Program

aOR: Adjusted odds ratio

CAI: Community-acquired infection

CI: Confidence interval

HAI: Healthcare-acquired infection

NS: Not significant

OR: Odds ratio

SD: Standard deviation

SIRS: Systemic inflammatory response syndrome

USD: US dollars

Declarations

Ethical approval and consent to participate

This research was classified as minimal risk and the study was approved by the ethics committees of the participating institutions and the Centro Internacional de Entrenamiento en Investigaciones Médicas (CIDEIM) ethics and research committee. Patient data was obtained retrospectively with permission of the participating institutions after approval by the ethics committees. According to the national legislation, consent to participate was not required.

Consent for publication

All authors agreed on the publication of the research.

Availability of supporting data

Not applicable

Competing interests

Maria V. Villegas has received consulting fees and research grants from Merck Sharp & Dohme, Pfizer, Merck SA, West SA and OpGen. Ernesto Martínez has received consulting fees from Pfizer, Merck Sharp and Dohme, Stendhal, Gilead/Gador, GSK and ABBVIE. Christian Pallares has received consulting fees and research grants from Merck Sharp & Dohme, Pfizer, Merck SA, West SA and OpGen. Cristhian Hernández-Gómez has received consulting fees from Merck Sharp & Dohme, Pfizer and West. Cristhian Hernández-Gómez participated in research activities until august 2018.

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Author's contributions

Cristhian Hernández-Gómez and Christian Pallares designed and implemented the study. Kevin Escandón-Vargas, Sergio Reyes, Soraya Salcedo, Lorena Matta, Ernesto Martínez, Sara Cobo, Laura Mora, Adriana Marín, Adriana Correa supported the implementation and discussed and analyzed the results. Cristhian Hernández-Gómez, Christian Pallares, Tobias Manuel Appel and María Virginia Villegas discussed and analyzed the results and wrote the paper.

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Tables

Table 1. Characteristics of involved institutions.

Institution*	A	B	C	D
City	Barranquilla	Cali	Cali	Cali
Number of beds	500	900	120	150
Type of hospital	Private	Public	Private	Private
Clinical area	General hospital	General hospital	General hospital	Cardiovascular and neurosurgery
Organ transplantation	No	Bone marrow	Bone marrow	No

*All general hospitals had emergency departments, general wards, intensive care units and general and specialized surgery.

Table 2. Distribution of baseline characteristics of patients exposed (Post-) and not exposed (Pre-) to the ASP.

Variable*	Pre-ASP <i>n</i> = 429 (48%)	Post-ASP <i>n</i> = 471 (52%)	<i>p</i> value
Sex			
Male	227 (53%)	258 (55%)	0.570
Female	202 (47%)	213 (45%)	
Age (years)			
18-20	13 (3%)	22 (5%)	0.450
21-31	50 (12%)	41 (9%)	
32-42	54 (13%)	50 (10%)	
43-53	45 (10%)	70 (15%)	
54-64	69 (16%)	90 (19%)	
65-75	160 (37%)	160 (34%)	
>75	39 (9%)	38 (8%)	
Origin of infection			
Community-acquired	221 (52%)	249 (53%)	0.685
Hospital-acquired	208 (48%)	222 (47%)	
Comorbidities			
Overall (at least one comorbidity)	288 (67%)	341 (72%)	0.085
Diabetes	76 (18%)	78 (17%)	0.646
Neurological illness	35 (8%)	72 (15%)	0.001
Chronic obstructive pulmonary disease	32 (7%)	18 (4%)	0.017
Abnormalities of the urinary tract	5 (1%)	4 (1%)	0.442
Cardiovascular disease	99 (23%)	136 (29%)	0.048
Immunosuppression	23 (5%)	40 (8%)	0.066
Kidney disease	40 (9%)	54 (11%)	0.294
Solid tumors	30 (7%)	34 (7%)	0.895

Abbreviation: ASP, antimicrobial stewardship program.

*Data are expressed as number (%) unless specified otherwise.

Table 3. Distribution of clinical variables of patients exposed (Post-) and not exposed (Pre-) to the ASP.

Variable*	Pre-ASP <i>n</i> = 429 (48%)	Post-ASP <i>n</i> = 471 (52%)	<i>p</i> value
SIRS at initiation of treatment	269 (63%)	321 (68%)	0.086
Sepsis at initiation of treatment	228 (53%)	300 (64%)	0.001
Septic shock at initiation of treatment	41 (10%)	21 (4%)	0.003
Length of stay before infection, days, mean (SD) (HAI patients only)	19.5 (+/- 24)	21.6 (+/-19)	0.029
Type of infection			0.112
Urinary tract infection	107 (25%)	144 (31%)	
Bloodstream infection	106 (25%)	131 (28%)	
Intra-abdominal infection	51 (12%)	50 (11%)	
Pneumonia	92 (21%)	78 (17%)	
Skin and soft tissue infection	73 (17%)	68 (14%)	
Hospital location when the infection was diagnosed			0.001
Emergency department	27 (6%)	11 (2%)	
Hospitalization	175 (41%)	220 (47%)	
Dialysis and chemotherapy units	7 (2%)	22 (5%)	
Intermediate care unit	23 (5%)	28 (6%)	
Intensive care unit	197 (46%)	190 (40%)	
Length of stay during infection, days, mean (SD)	14.0 (+/-8)	10.8 (+/-7)	<0.001
Time to initiation of empirical antibiotic therapy, hours, mean (SD)	5 (+/-5)	4 (+/-4)	0.037
Adequate dose of empirical treatment	33 (25%)	96 (86%)	<0.001
Adherence to empirical antibiotic therapy guidelines	31 (9%)	173 (45%)	<0.001
Post-empirical treatment complications	185 (43%)	166 (35%)	0.015
Change in empirical treatment	190 (52%)	263 (67%)	<0.001
Adequate de-escalation	23 (8%)	311 (92%)	<0.001
Post-targeted treatment complications	79 (18%)	82 (17%)	0.694
Clinical improvement at 72 hours of empirical treatment	227 (62%)	285 (73%)	0.299
Clinical improvement at 72 hours of targeted treatment	160 (73%)	229 (75%)	0.663

Clinical cure at the end of treatment	314 (74%)	438 (93%)	<0.001
Mortality	117 (28%)	65 (14%)	<0.001

Abbreviations: ASP, antimicrobial stewardship program; SD, standard deviation; SIRS, Systemic inflammatory response syndrome.

*Data are expressed as number (%) unless specified otherwise.

Table 4. Bivariate analysis of patients exposed (Post-) and not exposed (Pre-) to the ASP.

Variable	OR (95% CI / <i>p</i> value)
Exposure to an ASP program	4.90 (3.16-7.76 / <i>p</i> <0.01)
Sex	0.97 (0.66-1.41 / <i>p</i> =0.879)
Age	1.05 (0.56-1.86 / <i>p</i> =0.846)
Origin of infection (community- versus hospital-acquired)	0.65 (0.44-0.95 / <i>p</i> =0.021)
Comorbidities	1.22 (0.81-1.83 / <i>p</i> =0.290)
Sepsis	1.48 (1.01-2.16 / <i>p</i> =0.033)
Septic shock	0.20 (0.11-0.36 / <i>p</i> <0.001)
Time to initiate empirical antibiotic	1.23 (0.63-2.41 / <i>p</i> =0.504)
Change in empirical treatment	1.33 (0.89-1.98 / <i>p</i> =0.138)
Adherence to empirical antibiotic therapy guidelines	3.35 (1.88-6.34 / <i>p</i> <0.001)
Adequate dose of empirical treatment	1.48 (0.68-3.25 / <i>p</i> =0.272)
Post-empirical treatment complications	0.38 (0.25-0.59 / <i>p</i> <0.001)
Post-targeted treatment complications	1.10 (0.96-1.28 / <i>p</i> =0.062)
Septic shock after targeted therapy	0.23 (0.14-0.38 / <i>p</i> <0.001)
Adequate de-escalation	3.76 (2.21-6.60 / <i>p</i> <0.001)

Abbreviation: ASP, antimicrobial stewardship program; CI, confidence interval; OR, odds ratio.

Table 5. Logistic regression model in patients exposed (Post-) and not exposed (Pre-) to the ASP.

Variable	aOR (95% CI / <i>p</i> value)
Exposure to an ASP program	10.40 (1.21-89.41 / <i>p</i> =0.033)
Origin of infection (community- versus hospital-acquired)	0.77 (0.44-1.37 / <i>p</i> =0.386)
Sepsis	1.57 (0.82-3.01 / <i>p</i> =0.170)
Septic shock	0.81 (0.31-2.09 / <i>p</i> =0.669)
Post-empirical treatment complications	0.68 (0.27-1.72 / <i>p</i> =0.428)
Post-targeted treatment complications	0.49 (0.25-0.97 / <i>p</i> =0.041)
Change in empirical treatment	1.21 (0.57-2.59 / <i>p</i> =0.611)
Adherence to empirical antibiotic therapy guidelines	1.10 (0.49-2.47 / <i>p</i> =0.813)
Sepsis after targeted therapy	0.64 (0.25-1.64 / <i>p</i> =0.362)
Septic shock after targeted therapy	0.37 (0.13-1.07 / <i>p</i> =0.068)
Adequate de-escalation	0.52 (0.64-4.28 / <i>p</i> =0.550)

Abbreviation: aOR, adjusted odds ratio; ASP, antimicrobial stewardship program; CI, confidence interval.

Table 6. Cost analysis of patients exposed (Post-) and not exposed (Pre-) to the ASP.

Variable	Pre-ASP <i>n</i> = 429 (48%)	Post-ASP <i>n</i> = 471 (52%)	<i>p</i> value
Cost of stay during infection (USD) *	3,669	2,436	<0.001
Cost of exams and initial intervention (USD) *	275	181	<0.001
Cost of empirical therapy (USD) *	363	208	<0.001
Targeted therapy cost (USD) *	71	57	NS
Total infection cost (USD) *	4,156	2,952	<0.001

Abbreviation: ASP, antimicrobial stewardship program; NS, not significant.

*Average cost per patient

Figures

Figure 1

Study design