



Impact of a pharmacist-driven antimicrobial stewardship program in a private hospital in Costa Rica

José Pablo Díaz-Madriz,¹ Eugenia Cordero-García,² José Miguel Chaverri-Fernández,²
Esteban Zavaleta-Monestel,¹ Josué Murillo-Cubero,³ Hellen Piedra-Navarro,² Marian Hernández-
Guillén,² and Tiffany Jiménez-Méndez²

Suggested citation Díaz-Madriz JP, Cordero-García E, Chaverri-Fernández JM, Zavaleta-Monestel E, Murillo-Cubero J, Piedra-Navarro H, et al. Impact of a pharmacist-driven antimicrobial stewardship program in a private hospital in Costa Rica. *Rev Panam Salud Publica*. 2020;44:e57. <https://doi.org/10.26633/RPSP.2020.57>

ABSTRACT

Objective. To measure the impact generated by the implementation of the pharmacy-driven antimicrobial stewardship program of the Clínica Bíblica Hospital.

Methods. This is a retrospective observational study that evaluates the consumption of antibiotics for the periods before and during implementation of the Clínica Bíblica Hospital antimicrobial stewardship program, calculated by means of defined daily dose per 1 000 patient-days and days of therapy per 1 000 patient-days. In addition, bacterial resistance patterns for the periods 2014–2015 and 2016–2017 were compared.

Results. Consumption of most-used antibiotics was calculated, looking for trends that might be associated with the activities implemented by the Clínica Bíblica Hospital antimicrobial stewardship program. Comparing some of the antibiotics with the highest consumption in periods I and II, use of levofloxacin and ceftriaxone showed a decrease of 54.0% ($p < 0.001$) and 14.6% ($p = 0.003$), respectively, whereas there was an increase in the use of cefazolin of 4 539.3% ($p < 0.001$). Regarding percentage of bacterial resistance, in most bacterial isolates no statistically significant changes were observed between the two periods.

Conclusions. A reduction in the overall consumption of antibiotics has been achieved over time, most likely attributable to the antimicrobial stewardship program. However, this trend was not observed for all the antibiotics studied. The pattern of resistance among the commonly isolated microorganisms did not vary greatly between the periods studied, which suggests that either the antimicrobial stewardship program may have prevented an increase in bacterial resistance since its implementation, or that it is too soon to see impact on bacterial resistance.

Keywords

Antimicrobial stewardship; anti-infective agents; drug utilization; drug resistance, microbial; Costa Rica.

Antimicrobials are a group of successful drugs that have allowed a radical change in the health landscape, reducing historical morbidity and mortality by preventing infectious diseases from being the main cause of death (1–3).

However, in recent decades the indiscriminate use and abuse of these drugs in animals and humans has generated problems, including adverse reactions in patients, leading to an increase

of unnecessary expenses for the health system and the appearance of bacterial resistance (4–9).

Health centers are an ideal setting for the appearance of multidrug-resistant bacteria (7). Antimicrobial stewardship programs (AMS) have been established to address this problem, and to set standards and guidelines for health care professionals (10).

¹ Hospital Clínica Bíblica, San José, Costa Rica. ✉ José Pablo Díaz-Madriz, jp.diazm27@gmail.com

² University of Costa Rica, San Pedro, Costa Rica

³ Universidad de Ciencias Médicas (UCIMED), San José, Costa Rica

The aim of this study was to measure the impact generated by the AMS of the Clínica Bíblica Hospital (AMS-HCB), one of the first hospitals in Central America to implement this initiative. The AMS-HCB is pharmacy driven and works without restrictions on the use of antimicrobials. The main practices implemented by this program are prospective audit and feedback, clinical guidelines development, and educational sessions.

MATERIALS AND METHODS

This is a retrospective observational study conducted at the Clínica Bíblica Hospital, a 68-bed private health center located in San José, Costa Rica. The records of patients who received antibiotic therapy with any of the following medications were analyzed: meropenem, ertapenem, moxifloxacin, levofloxacin, ciprofloxacin, cefuroxime, ceftriaxone, ceftazidime, cefazolin, cefalotin, vancomycin, ampicillin/sulbactam, and linezolid.

The consumption levels for the period before implementation of the AMS, or period I (April 2013–March 2015), and during the implementation of the AMS, or period II (April 2015–March 2017), were determined by calculating the defined daily dose (DDD¹) per 1 000 patient-days and days of therapy (DOT²) per 1 000 patient-days (1, 11–13). The results for both periods were compared using IBM SPSS software. When calculating the values of DDD per 1 000 patient-days and DOT per 1 000 patient-days, the monthly average of each of the antibiotics was calculated and subjected to a descriptive statistical analysis. The Kruskal-Wallis nonparametric test was performed (14–16).

In addition, bacterial resistance patterns were compared for the periods 2014–2015 and 2016–2017. These patterns were based on the resistance reports on bacteria cultivated in the hospital during these periods, as reported by the Clínica Bíblica Hospital's Clinical Laboratory and Infection Prevention Committee. The resistance reports were obtained from the VITEK-2[®] automated identification and antibiotic susceptibility testing system. These data were analyzed using the chi-squared test, to identify statistically significant changes in resistance that might be associated with the implementation of the AMS.

Regarding the data analysis, the first isolate of each infectious episode was considered, as well as the verification of the data by a microbiologist, and recommendations issued by the Clinical and Laboratory Standards Institute (CLSI) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) (17, 18).

For *Pseudomonas aeruginosa* and *Enterococcus faecalis*, elimination of some reports of resistance was required, due to the fact that they might have intrinsic resistance for some of the antibiotics studied. In addition, the report of colistin resistance was eliminated for all bacteria, as it is a more restricted antibiotic and requires a comprehensive analysis of each case before its use (19).

Information for the study was obtained from the electronic clinical records from the Clínica Bíblica Hospital's Hospitalized Patients Management system, Integrated Hospital Management System, and pharmacy records. The bacterial identification and

resistance test results were also extracted through the computer system, along with other patient data of interest to the study. There was also access to the physical clinical records of these patients, as necessary.

It is important to mention that the ethical use of the data and patient confidentiality were guaranteed at all times. This work was approved by the Clínica Bíblica Hospital and the Scientific Ethics Committee of the University of Costa Rica (VI-3253-2018).

RESULTS

DDD

With the data obtained from the study, a DDD calculation was made for every 1 000 patient-days for the 13 most-used antibiotics in the hospital. Table 1 compares the average use of antibiotics in the Clínica Bíblica Hospital in the two periods. Broad-spectrum antibiotics such as quinolones, third-generation cephalosporins, and carbapenems were found to be the most widely used.

Comparing the four antibiotics with the highest consumption in periods I and II, the DDD per 1 000 patient-days for levofloxacin showed a decrease of 54.0% ($p < 0.001$). Similarly, although with a smaller magnitude of change, ceftriaxone use decreased by 14.6% ($p = 0.003$), while the decrease in ciprofloxacin use was not statistically significant (1.5%, $p = 0.47$). In contrast, there was a statistically significant increase in the use of ertapenem by 15.6% ($p = 0.041$).

Although their consumption was lower, there was an upward trend in use of some of the reduced-spectrum antibiotics following the implementation of the AMS-HCB. Such was the case for cefazolin and cefuroxime, which showed a significant increase in the DDD per 1 000 patient-days of 4 539.3% ($p < 0.001$) and 406.4% ($p < 0.001$), respectively. In addition, there were statistically significant decreases in the consumption of cefalotin

TABLE 1. Comparison of the changes in average of consumption as measured by DDD per 1 000 patient-days for the hospitalized population between periods I and II in Clínica Bíblica Hospital

	DDD/1 000 patient-days				<i>p</i>
	Period I	Period II	Magnitude of change	%	
Amp/sulb	119.5	123.3	▲ 3.8	▲ 3.2	0.741
Cefalotin	26.4	18.9	▼ 7.5	▼ 28.4	0.006
Cefazolin	1.1	49.4	▲ 48.3	▲ 4 539.3	<0.001
Ceftazidime	27.0	25.2	▼ 1.8	▼ 6.6	0.523
Ceftriaxone	223.3	190.6	▼ 32.7	▼ 14.6	0.003
Cefuroxime	26.0	131.6	▲ 105.6	▲ 406.4	<0.001
Ciprofloxacin	218.8	215.6	▼ 3.2	▼ 1.5	0.470
Ertapenem	151.3	174.9	▲ 23.6	▲ 15.6	0.041
Levofloxacin	325.6	149.9	▼ 175.7	▼ 54.0	<0.001
Linezolid	69.0	79.8	▲ 10.8	▲ 15.5	0.174
Meropenem	108.4	86.8	▼ 21.6	▼ 19.9	0.076
Moxifloxacin	84.1	80.8	▼ 3.3	▼ 3.9	0.496
Vancomycin	74.7	56.1	▼ 18.6	▼ 25.0	0.029

DDD, defined daily dose; Amp/sulb, ampicillin/sulbactam; ▼ decrease; ▲ increase.

Source: Prepared by the authors based on data from Clínica Bíblica Hospital Antimicrobial Stewardship Program

¹ DDD is a clinical parameter established by the World Health Organization that represents the average daily dose of an antibiotic for a standard patient.

² DOT is defined as the number of days a patient has received antibiotics regardless of the prescribed dose.

and vancomycin by 28.4% ($p = 0.006$) and 25.0% ($p = 0.029$), respectively.

DOT

For the 13 most-used antibiotics, calculated as DOT per 1 000 patient days, between period I and period II there was an apparent reduction of 3.2% ($p = 0.108$). This is equivalent to that calculated by DDD per 1 000 patient-days, 3.2% ($p = 0.174$), both not statistically significant.

According to DOT per 1 000 patient-days, there was a highly significant decrease in consumption of ceftriaxone and levofloxacin, by 19.1% ($p < 0.001$) and 49.9% ($p < 0.001$), respectively (Table 2). There was also a statistically significant decrease in the consumption of meropenem and vancomycin, by 19.1% ($p = 0.02$) and 30.7% ($p = 0.005$), respectively. On the other hand, there was a significant increase of 17.4% ($p = 0.037$) in the consumption of ertapenem, the antibiotic with the second highest DOT per 1 000 patient-days in both periods I and II. This is similar to the results obtained according to DDD per 1 000 patient days.

In addition, there were other important changes for cefazolin consumption, with an increase of 2 215.1% ($p < 0.001$), and for cefuroxime, with an increase of 309.8% ($p < 0.001$). These results are consistent with the data for DDD per 1 000 patient-days.

Antibiotic resistance

The bacteria with greater clinical relevance or a greater number of isolates were analyzed for each period (Table 3) and the number of final strains isolated obtained, which was then used to perform comparisons of antibiotic resistance profiles for each bacteria.

An example of the analysis done for each of the bacteria is shown in Table 4, which presents the resistance profile of *Staphylococcus epidermidis* against a range of antibiotics for the periods 2014–2015 and 2016–2017. A highly significant decrease in the resistance of *S. epidermidis* to rifampicin was observed with a magnitude of change of 36% ($p < 0.001$). In addition, significant differences were found in the resistance of *E. faecalis* to gentamicin, a decrease of 18% ($p = 0.032$); as well as a decrease in resistance of *Staphylococcus haemolyticus* to rifampicin (44%, $p = 0.004$), and an increase in resistance to trimethoprim/sulfamethoxazole (36%, $p = 0.038$). For the rest of the bacteria, no statistically significant changes were found in the percentages of resistance comparing the two periods.

DISCUSSION

In 2015, the Clínica Bíblica Hospital implemented a pharmacist-driven antimicrobial stewardship program (20, 21), the AMS-HCB. Since its implementation, it has been constantly and actively monitored by a multidisciplinary team consisting of a clinical pharmacist (director), an infectious disease physician, a microbiologist, and the hospital's assistant chief medical officer.

In 2015, when high levels of consumption of broad-spectrum antibiotics were detected in the hospital, one of the main problems was the incorrect use of ceftriaxone and levofloxacin in surgical prophylaxis. The AMS team executed educational activities to promote greater use of first-generation cephalosporins such as cefazolin, since these were the drugs of

TABLE 2. Comparison of the changes in average consumption as measured by DOT per 1 000 patient-days for the hospitalized population between periods I and II in Clínica Bíblica Hospital

	DOT/1 000 patient-days				<i>p</i>
	Period I	Period II	Magnitude of change	%	
Amp/sulb	51.0	43.3	▼ 7.8	▼ 15.2	0.364
Cefalotin	32.8	26.0	▼ 6.8	▼ 20.7	0.055
Cefazolin	2.2	50.1	▲ 48.0	▲ 2 215.1	<0.001
Ceftazidime	23.8	25.7	▲ 1.9	▲ 7.8	0.711
Ceftriaxone	265.1	214.5	▼ 50.6	▼ 19.1	<0.001
Cefuroxime	2.0	8.0	▲ 6.1	▲ 309.8	<0.001
Ciprofloxacin	48.3	57.6	▲ 9.3	▲ 19.3	0.274
Ertapenem	125.1	146.9	▲ 21.8	▲ 17.4	0.037
Levofloxacin	74.3	37.2	▼ 37.1	▼ 49.9	<0.001
Linezolid	44.1	61.0	▲ 16.9	▲ 38.4	0.039
Meropenem	80.7	65.3	▼ 15.4	▼ 19.1	0.020
Moxifloxacin	42.4	47.1	▲ 4.7	▲ 11.1	0.496
Vancomycin	71.3	49.4	▼ 21.9	▼ 30.7	0.005

DOT, days of therapy; Amp/sulb, ampicillin/sulbactam; ▼ decrease; ▲ increase.

Source: Prepared by the authors based on data from Clínica Bíblica Hospital Antimicrobial Stewardship Program

TABLE 3. Frequency of isolation of the bacteria analyzed in Clínica Bíblica Hospital, 2014–2015 and 2016–2017

	Total strains isolated 2014–2015*	Total strains isolated 2016–2017*
Gram-negative bacilli		
<i>Escherichia coli</i>	137	178
<i>Pseudomonas aeruginosa</i>	87	94
<i>Klebsiella pneumoniae</i>	48	62
<i>Stenotrophomonas maltophilia</i> **	20	13
Gram-positive cocci		
<i>Staphylococcus aureus</i>	81	78
<i>Staphylococcus epidermidis</i>	45	51
<i>Enterococcus faecalis</i>	35	37
<i>Staphylococcus haemolyticus</i> **	16	15

* The number of final strains corresponds to the number of strains that were included in the final analysis of the data, following the recommendations of the Clinical and Laboratory Standards Institute (CLSI) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC).

** Those isolates with fewer than 30 reported strains should be interpreted with caution since they may not represent faithfully the resistance profile of the group of bacteria analyzed.

Source: Prepared by the authors based on data from Clínica Bíblica Hospital Antimicrobial Stewardship Program

choice for surgical antibiotic prophylaxis, as indicated by the clinical guideline implemented at that time. These strategies explain the significant increase in the use of cefazolin (2 215.1%, $p < 0.001$) and the decrease in the consumption of ceftriaxone (19.1%, $p < 0.001$), and partially explain the decrease of levofloxacin (49.9%, $p < 0.001$), according to the consumption calculated in DOT (Figure 1). Ertapenem is another antibiotic that was recommended to be avoided in surgical prophylaxis, as well as in a wide number of other indications. However, this is the only antibiotic that did not show a reduction in consumption. On the contrary, it increased over time (17.4%, $p = 0.037$). This suggests that different strategies are needed in order to control the overprescription of ertapenem.

The decrease in the consumption of meropenem (19.1%, $p = 0.02$) represents valuable progress in the initiative to

TABLE 4. Comparison of the reports of antibiotic resistance for *Staphylococcus epidermidis* in Clínica Bíblica Hospital, 2014–2015 and 2016–2017

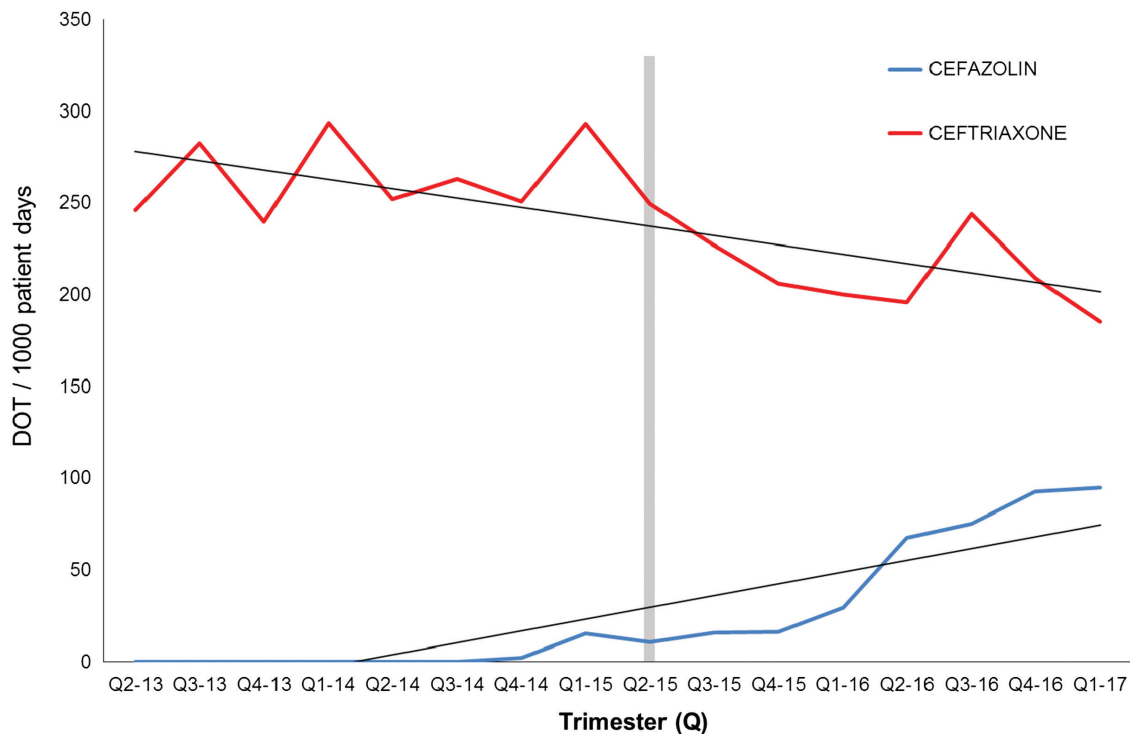
<i>Staphylococcus epidermidis</i>	Period 2014–2015			Period 2016–2017			Magnitude of change	p
	n resistant*	n total	%R*	n resistant*	n total	%R*		
Benzylpenicillin	45	45	100	40	42	95	▼5	0.139
Beta-lactamases	39	45	87	37	43	86	▼1	0.932
Ciprofloxacin	33	45	73	38	51	75	▲2	0.896
Clindamycin	23	45	51	24	51	47	▼4	0.692
Erythromycin	37	45	82	41	51	80	▼2	0.819
Gentamicin	15	45	33	23	51	45	▲12	0.239
Levofloxacin	33	45	73	38	51	75	▲2	0.896
Linezolid	0	45	0	0	51	0	0	-
Moxifloxacin	18	45	40	20	51	39	▼1	0.937
Oxacillin MIC	36	45	80	43	50	86	▲6	0.435
Inducible resistance to clindamycin	3	45	7	3	51	6	▼1	0.874
Rifampicin	27	45	60	12	51	24	▼36	<0.001
Tetracycline	30	45	67	38	51	75	▲8	0.399
Tigecycline	0	45	0	0	43	0	0	-
Trimethoprim/sulfamethoxazole	18	45	40	26	51	51	▲11	0.281
Vancomycin	0	45	0	0	51	0	0	-

R, resistance; n, number of isolations; ▼ decrease; ▲ increase.

* Includes resistant strains with intermediate sensitivity.

(-) Statistical significance was not calculated because the resistance of this bacteria to these antibiotics is a constant.

Source: Prepared by the authors based on data from Clínica Bíblica Hospital Antimicrobial Stewardship Program

FIGURE 1. Trend in the trimester averages of days of therapy (DOT) per 1 000 patient days for cefazolin and ceftriaxone in Clínica Bíblica Hospital for the period 2013–2017, before and during implementation of the antimicrobial stewardship program

Source: Prepared by the authors based on data from Clínica Bíblica Hospital Antimicrobial Stewardship Program

improve the use of antimicrobials, since meropenem is considered an antibiotic of last resort. Regarding *P. aeruginosa*, its resistance to meropenem has increased in the country; thus, strategies to optimize the use of this antibiotic and of

all carbapenems should be reinforced (22). Multiple studies have compared the relationship between the consumption of antibiotics and the reported rates of resistance. In the case of *P. aeruginosa*, it has a high capacity to acquire new resistance

mechanisms under selective antibiotic pressure, including loss of outer membrane proteins, efflux pumps, and production of certain beta-lactamases, among others. In vitro and in vivo studies have documented that exposure to carbapenems increases the risk of carbapenem-resistant *P. aeruginosa*, which is also associated with cross-resistance to other antibiotics (23).

On the other hand, the consumption of linezolid increased (38.4%, $p = 0.039$), while vancomycin consumption decreased (30.7%, $p = 0.005$). This change can be related to the preferences of the prescriber, since these are two antibiotics that are used for Gram-positive infections. Linezolid may be preferred over vancomycin based on some reports that show similar activity for methicillin-resistant *Staphylococcus aureus* specific infections with less nephrotoxicity. It is also dosed easier than vancomycin, which must be adjusted according to the pharmacokinetic profile of each patient. In addition, conversion to oral administration is easily performed in the case of linezolid, and no dosage adjustment is necessary in case of renal failure. Its resistance profile has not changed and it remains 100% sensitive (24–26).

One of the main reasons why AMSs are necessary in hospitals is the constant growth of resistance (27). A non-increase in resistance, as shown in the results, is considered a positive result, suggesting that the actions of the AMS are having an impact on physicians' prescriptions. However, it is necessary to continue monitoring the effects over time, since positive and conclusive results usually are seen in a 4.8-year period after the intervention (28, 29). Despite the few significant changes regarding the patterns of resistance in this study, a longer follow-up period is

generally required to appreciate changes in the microbiota of a hospital center (28, 29).

Some limitations include the design of the study, since it cannot assure that the AMS is the direct cause or the only cause of the changes described in the results. Variations in the level of antimicrobial resistance can also be influenced by the actions of the hospital's Infection Prevention Committee, as well as other factors external to this hospital, such as the use of antibiotics in other health facilities.

Nonetheless, when determining the consumption by means of DDD per 1 000 patient-days and DOT per 1 000 patient-days, it is evident that reductions in the overall consumption of antibiotics have been achieved over time, possibly attributable to AMS implementation. However, this is not a common trend for all antibiotics, and the continuation of the program should be evaluated in the near future. The development and implementation of more clinical guidelines is the next step to cover more antibiotics used in the hospital setting.

Author contributions. All authors contributed to the study design, data analysis and interpretation, and writing of the paper. All authors reviewed and approved the final version.

Conflicts of interest. None declared.

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Manuscript received on 25 October 2019. Revised version accepted for publication on 2 April 2020.

Impacto de un programa de optimización del uso de antimicrobianos conducido por la farmacia de un hospital privado en Costa Rica

RESUMEN

Objetivo. Medir el impacto de la ejecución de un programa de optimización del uso de antimicrobianos conducido por la farmacia del Hospital Clínica Bíblica.

Métodos. En este estudio retrospectivo y de observación se evaluó el consumo de antibióticos antes y después de la ejecución del programa de optimización del uso de antimicrobianos en el Hospital Clínica Bíblica. El consumo se calculó tomando como base la dosis diaria por 1.000 días-paciente y los días de tratamiento por 1.000 días-paciente. Además, se compararon los perfiles de resistencia bacteriana en los períodos 2014-2015 y 2016-2017.

Resultados. Se calculó el consumo de los antibióticos más usados para establecer las tendencias que podrían estar relacionados con las actividades ejecutadas por el programa de optimización del uso de antimicrobianos del Hospital Clínica Bíblica. Se compararon algunos de los antibióticos de mayor consumo en los períodos I y II, el uso de la levofloxacina y la ceftriaxona mostró una disminución de 54,0% ($p < 0,001$) y 14,6% ($p = 0,003$), respectivamente, mientras que se evidenció un aumento en el uso de la cefazolina de 4.539,3% ($p < 0,001$). Con respecto al porcentaje de resistencia bacteriana, no se encontró ningún cambio estadísticamente significativo entre los dos períodos para la mayoría de las cepas bacterianas aisladas.

Conclusiones. Con el transcurso del tiempo se ha logrado una disminución en el consumo de antibióticos en general, probablemente relacionada con el programa de optimización del uso de antimicrobianos. Sin embargo, esta tendencia no se observó en todos los antimicrobianos analizados. No se evidenció una variación significativa en los patrones de resistencia entre los microorganismos aislados comúnmente entre los períodos comparados, lo que puede significar dos cosas: que el programa de optimización del uso de antimicrobianos podría haber evitado un aumento de resistencia bacteriana desde que se puso en marcha o que es demasiado pronto para que se evidencie un impacto en la resistencia bacteriana.

Palabras clave

Programas de optimización del uso de los antimicrobianos; antiinfecciosos; utilización de medicamentos; farmacoresistencia microbiana; Costa Rica.

Impacto de um programa de gerenciamento do uso de antimicrobianos por profissionais farmacêuticos em um hospital particular na Costa Rica

RESUMO

Objetivo. Mensurar o impacto da implantação de um programa de gerenciamento do uso de antimicrobianos por profissionais farmacêuticos em um hospital particular.

Métodos. Trata-se de um estudo observacional retrospectivo para avaliar o uso de antibióticos no período anterior e posterior à implantação do programa de gerenciamento do uso de antimicrobianos no Hospital Bíblica Clínica, em San José, Costa Rica. O consumo dos medicamentos foi calculado com base na dose diária definida por 1.000 pacientes-dia e dias de tratamento por 1.000 pacientes-dia. Foi realizada uma comparação dos padrões de resistência bacteriana entre os períodos 2014–2015 e 2016–2017.

Resultados. O consumo dos antibióticos mais utilizados foi calculado visando identificar possíveis tendências associadas às ações do programa de gerenciamento do uso de antimicrobianos implantado no hospital. A comparação do consumo de alguns dos antibióticos mais utilizados no primeiro e no segundo períodos considerados apontou uma redução de 54,0% no uso de levofloxacina ($p < 0,001$) e 14,6% no uso de ceftriaxona ($p = 0,003$), com um aumento de 4.539,3% no uso de cefazolina ($p < 0,001$). Com relação à resistência bacteriana, não se observou variação estatisticamente significativa na maioria dos isolados bacterianos entre os dois períodos.

Conclusões. Houve redução no consumo de antibióticos em geral, provavelmente atribuível ao programa de gerenciamento do uso de antimicrobianos. Porém, esta mesma tendência não foi observada para todos os antibióticos estudados. Não houve variação importante no padrão da resistência dos microrganismos mais frequentemente isolados entre os períodos estudados. Isso indica que o programa de gerenciamento do uso de antimicrobianos implantado possivelmente evitou o aumento da resistência bacteriana ou que é ainda muito cedo para se observar o impacto na resistência bacteriana.

Palavras-chave

Gestão de antimicrobianos; anti-infecciosos; uso de medicamentos; resistência microbiana a medicamentos; Costa Rica.