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Towards implementing an antibiotic stewardship programme (ASP) in Ecuador: evaluating antibiotic consumption and the impact of an ASP in a tertiary hospital according to World Health Organization (WHO) recommendations

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ABSTRACT

Objectives: Ecuador is a lower-to-middle-income country not yet adherent to World Health Organization (WHO) antibiotic stewardship strategies, and data regarding basic metrics are still lacking.
Methods: We conducted a retrospective study of an antibiotic stewardship programme (ASP) consisting of restrictive measures on carbapenem dispensing pending required pre-authorisation and expert audit. We evaluated antibiotic consumption and its relationship to carbapenem resistance at a 610-bed, tertiary-level hospital in Quito, Ecuador. We used prescription data from 2010–2017 and converted them into defined daily doses (DDD). We then correlated these findings with the nature of service provided and antibiotic resistance data from the microbiology laboratory. We used descriptive statistics and interrupted time series (ITS) analysis.
Results: Throughout the study period, we analysed 16 984 355 prescriptions of 8 191 418.57 g of antibiotics (5 760 479.37 DDD). The in-hospital mean antibiotic prescription rate was 148.8 ± 14.8 DDD/100 occupied bed-days and 293.5 ± 65.3 DDD/100 occupied bed-days in the ICU. First-, second- and third-line antibiotic consumption was 38%, 52% and 10%, respectively. Our hospital data showed a high rate of antibiotic prescription in all hospital areas, mainly broad-spectrum antibiotics. Regarding the ASP introduced in 2016, ITS analysis showed a change in the outcome level immediately following the introduction for imipenem [–3.97; 95% confidence interval (CI) –5.31 to –2.61] but not for meropenem (0.66; 95% CI –0.37 to 1.71).
Conclusion: Although our institution's ASP was successful in reducing imipenem consumption, a more embracing plan is required for further interventions to avoid unexpected effects.

1. Introduction

Antibiotic resistance is the result of multiple factors. There are external factors such as the use of antibiotics in livestock and agriculture. Moreover, there are internal factors to healthcare facilities, such as selective pressure due to inadequate or excessive use of antibiotics. Whatever the cause, antibiotic resistance poses a global threat, with frightening projections regarding increasing mortality rates and costs [1].

Of particular importance, there is evidence that antibiotic resistance is a more significant problem in lower-to-middle-income countries (LMICs). The World Health Organization (WHO) and its regional office, the Pan American Health Organization (PAHO), presented recommendations for the implementation of several measures, including antibiotic stewardship programmes (ASPs), as a strategy to deal with this pressing problem [2,3]. Although ASPs are the cornerstone of this strategy, their implementation faces several cultural, administrative and cost barriers [4]. Furthermore, the metrics to measure the impact of ASPs are still debatable [5].

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Hospital Carlos Andrade Marín, the largest social security hospital (610 beds), is located in Quito, Ecuador. Ecuador is a LMIC not yet adherent to WHO antibiotic stewardship strategies, and data regarding basic metrics are still lacking. We thought to provide these metrics using WHO proposed methodology and to assess the impact of an ASP consisting of restrictive measures on carbapenem dispensing pending required pre-authorisation and expert audit in the most important hospital in the country to help enrol Ecuador in the global war against antibiotic resistance.

2. Methods

2.1. Setting and design

We developed a descriptive, retrospective study approved by our institution's ethical committee. We extracted data from the dedicated in-house electronic health record (EHR) of a tertiary medical centre, which has 610 beds and attends an average of 26 582 patients per year. In this study, we reviewed the following antibiotics according to the Anatomical Therapeutic Chemical (ATC) classification system: J01–Antibacterials for systemic use and its subgroups, such as J01A–Tetracyclines; J01B–Amphenicols; J01C–β-Lactam antibacterials, penicillins; J01D–Other β-lactam antibacterials; J01E–Sulfonamides and trimethoprim; J01F–Macrolides; lincosamides and streptogramins; J01G–Aminoglycoside antibacterials; J01M–Quinolone antibacterials; J01R–Combinations of antibacterials; and J01X–Other antibacterials.

2.2. Measurement of antibiotic consumption

We calculated the defined daily doses (DDD) of each antibiotic based on the WHO ATC/DDD classification (https://www.whocc.no/atc_ddd_index/), current as of December 2018. In summary, we calculated DDD/100 occupied bed-days and captured antibiotic use data from the EHR after dispensing [2,4].

To calculate DDD/bed-days, we assumed a constant hospital capacity of 610 beds and an average annual discharge of 26 582 patients.

Antimicrobial agents were defined as first-line antimicrobials (i.e. amoxicillin, ampicillin, trimethoprim/sulfamethoxazole, metronidazole and doxycycline), second-line antimicrobials (i.e. ampicillin/sulbactam, amoxicillin/clavulanic acid, macrolides, lincosamides, second- or third-generation cephalosporins, and quinolones) and third-line antimicrobials (i.e. piperacillin/tazobactam, carbapenems, polymyxin, vancomycin and linezolid) [5]. The study excluded antifungal and antiviral agents.

We did not further analyse data after 2018 due to changes in the EHR as well as changes in antibiotic consumption patterns during COVID-19 (coronavirus disease 2019) [6]. We excluded paediatric patients and patients seen as outpatients in the emergency department; moreover, enrolled patients only contributed to the study during their in-hospital stay.

We stratified our results based on intensive care unit (ICU), clinical and surgical patients for the analysis, assuming that this could be a possible confounder. When we performed this stratification, we considered the increased numbers of ICU beds and patients discharged throughout this period. For the clinical and surgical settings, there was no significant change in capacity.

2.3. Antibiotic resistance

We also extracted data regarding antibiotic resistance that our institution sent to the Antimicrobial Resistance Surveillance Network (REDNARBEC), a programme designed by the WHO to monitor microbial populations worldwide [7]. The available data corresponded to the years 2010, 2016 and 2017. Information for the period 2011–2015 is not available since we did not collect data in a standardised format to send to the WHONET system.

2.4. Antibiotic stewardship programme (ASP)

In the year 2016, our institution implemented an embryonic ASP to reduce hospital antibiotic costs. Our infection control committee produced a list of carbapenems and established rules restricting access to them. Furthermore, if the pharmacy dispensed one of these antibiotics, the committee would review the clinical scenario and discuss the appropriateness of use. Only carbapenems and no other antibiotics were included in the restricted list.

2.5. Data analysis

We used MySQL Database Management Tool and R for analysis and graphical elaboration. We conducted univariate analysis according to the nature of the variables of interest (categorical or continuous) using classical parametric tests since all of the data followed a normal distribution. For multivariate analysis, we used logistic or linear regression as appropriate.

To assess the effect of the intervention, a model with interrupted time series (ITS) design was used: $Y_t = \beta_0 + \beta_1 \text{time}_t + \beta_2 \text{post}_t + \beta_3 \text{post\_int}_t + \varepsilon$, where β_0 is the starting level of outcome Y, β_1 is the pre-period slope, β_2 is the change in level at time intervention, β_3 is the change in slope in the post-period, int represents the ASP (intervention), time is the time point t incremented by one for each subsequent time point, and post equals one at the time immediately following the intervention. The post_int is the variable that equals zero until the time (int + 1) and is incremented by one for each subsequent time point, and ε is the error term [8,9]. We looked for significant *P*-values in β_2 to indicate an immediate treatment effect and in β_3 to indicate a treatment effect over time. We assumed that the intervention would produce immediate and persistent results [10,11]. We used time series for comparing trends in carbapenem use with two adjacent periods identified as segments. Regression analysis adapted for segmented time series assessed changes in imipenem and meropenem usage trends.

3. Results

Throughout the study period, we analysed 16 984 355 prescriptions of 8 191 418.57 g of antibiotics (5 760 479.37 DDD). The in-hospital mean ± standard deviation antibiotic prescription rate was 148.8 ± 14.8 DDD/100 occupied bed-days and 293.5 (65.3) DDD/100 occupied bed-days in the ICU.

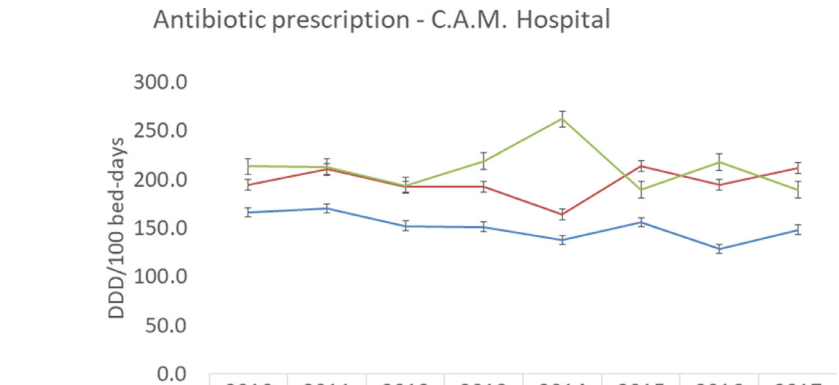
β-Lactams (J01C–JO1D) accounted for 60% of the total prescription of antibiotics in hospitalised patients, according to levels 2 and 3 of the ATC/DDD code. In contrast, those with the least prescription were tetracyclines (J01A) and aminoglycosides (J01G). First-, second- and third-line antibiotic consumption was 38%, 52% and 10%, respectively.

According to level 4 of the ATC/DDD code, we observed that within the group of β-lactams (J01C), the greater prescription volume corresponded to the group of broad-spectrum penicillins combined with β-lactamase inhibitors (J01CR), without antipseudomonal activity. Other β-lactams, particularly cephalosporins (J01DB, J01DD, J01DE) and carbapenems (J01DH), were the second most prescribed antibiotics. Macrolides (J01FA) and lincosamides (J01FF) also had a high consumption as did nitrofurans (J01XE) and glycopeptides (J01XA). Finally, fluoroquinolones (J01MA) were also among the most prescribed antibiotics for hospitalised patients (Table 1).

Table 1
Antibiotic consumption according service (clinical, surgical and ICU) and year in DDD/occupied bed-days

Service	Year	J01DB, J01DC, J01DD, J01DE– Cephalosporins	J01DB– First-generation cephalosporins	J01DD– Third-generation cephalosporins	J01DE– Fourth-generation cephalosporins	J01DH– Carbapenems	J01E– Sulfonamides	J01F– Macrolides, lincosamides	J01FA– Macrolides	J01FF– Lincosamides
Clinical (internal medicine)	2010	22.5	0.5	15.7	6.3	4.5	7.1	21.6	13.5	8.1
	2011	25.9	0.5	18.8	6.5	3.1	12.3	25.4	16.7	8.7
	2012	22.4	0.2	16.6	5.6	4.3	18.6	16.6	7.0	9.6
	2013	15.3	0.4	13.4	1.5	3.9	10.5	18.9	13.8	5.1
	2014	14.9	0.5	14.1	0.3	4.9	13.1	19.9	13.7	6.3
	2015	11.8	0.2	10.2	1.4	6.6	14.6	18.2	11.9	6.3
	2016	8.0	0.1	6.9	0.9	4.1	14.9	17.7	14.1	3.6
	2017	15.9	0.3	12.6	3.0	4.5	13.9	19.0	12.6	6.4
General surgery	2010	31.8	13.3	17.0	1.5	4.7	2.7	2.7	1.3	1.4
	2011	31.0	14.5	15.5	0.9	7.3	2.8	2.7	1.2	1.5
	2012	28.8	11.4	15.9	1.5	6.7	3.7	2.2	0.8	1.4
	2013	21.9	8.0	13.3	0.7	8.6	4.2	2.0	1.0	1.0
	2014	20.1	6.5	13.5	0.1	11.0	5.9	2.2	1.3	0.9
	2015	21.2	5.5	13.7	1.9	14.7	3.2	2.4	1.4	1.0
	2016	25.9	8.2	16.2	1.5	6.0	3.3	2.4	1.1	1.3
	2017	32.4	13.2	15.7	3.5	6.5	2.8	4.0	1.3	2.6
ICU	2010	43.8	11.1	17.0	15.7	45.0	2.7	5.7	3.8	1.9
	2011	37.5	8.8	16.1	12.6	47.3	7.1	6.6	5.4	1.1
	2012	25.2	6.3	15.8	3.1	42.6	4.0	9.7	7.2	2.5
	2013	23.1	7.5	15.0	0.6	44.0	5.9	12.2	10.9	1.3
	2014	31.3	9.8	20.9	0.5	44.0	13.2	19.3	15.3	4.0
	2015	23.3	9.5	5.3	8.5	47.3	6.4	11.0	8.7	2.3
	2016	17.2	8.8	6.4	2.0	48.0	5.1	14.7	12.0	2.7
	2017	23.3	9.5	5.3	8.5	47.3	6.4	11.0	8.7	2.3
P-value (ANOVA)		**<0.001**	**<0.01**	**0.385**	**0.032**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Post-hoc tests										
Surg-Clin		**0.005**	<0.001	0.65	0.60	**0.080**	<0.001	<0.001	<0.001	**1.0**
Surg-UTI		**0.850**	0.54	0.36	0.03	**<0.001**	0.123	<0.001	0.02	**0.001**
Clin-UTI		**0.001**	<0.001	0.88	0.18	**<0.001**	<0.001	<0.001	<0.001	**0.001**

ICU, intensive care unit; DDD, defined daily doses; ANOVA, analysis of variance.



	2010	2011	2012	2013	2014	2015	2016	2017
General Surgery	194.7	210.7	192.4	192.5	164.5	213.8	194.5	211.8
ICU	213.4	212.8	193.9	218.9	262.1	189.5	217.9	189.5
Internal Medicine	166.2	170.2	152.5	151.3	137.8	155.9	128.8	148.2

Fig. 1. Antibiotic consumption in defined daily doses (DDD)/beds-days for clinical (internal medicine), surgical and intensive care unit (ICU) services, by year. Data are the mean and 95% confidence interval.

When comparing the consolidated prescription of different areas, the consumption of clinical services was lower than that of surgical services and the ICU. Despite a statistically significant point in 2014, the surgical and ICU antibiotic consumption was similar and exhibited higher values than clinical services (Fig. 1).

The ICU is the service that registered the highest prescription of antibiotics in the entire hospital. Regarding the group 'Other β-lactam antibacterials (J01D)', when comparing the prescription among ICU, clinical and surgical services we found significant differences within this therapeutic group, with clinical services consuming significantly less than surgical and ICU services ($P = 0.036$) (Table 1).

On the other hand, extended-spectrum penicillins with and without antipseudomonal activity, third- and fourth-generation cephalosporins, and carbapenems differed when comparing the groups ($P = 0.001$) between the ICU and the other services. We found significant differences in the prescription of first-generation cephalosporins, sulfonamides and macrolides between clinical services and the other two services. There were no differences in terms of carbapenem prescription between surgical and clinical services ($P = 0.08$) (Table 1).

Regarding the ASP introduced in 2016, the ITS analysis showed a change in the outcome level immediately following the introduction for imipenem [–3.97; 95% confidence interval (CI) –5.31 to –2.61] but not for meropenem (0.66; 95%CI –0.37 to 1.71). These findings are expressed graphically in Fig. 2, signalling the ASP intervention (vertical dotted lines) and the added impact over ceftriaxone (–1.12; 95% CI –2.71 to 0.47) and piperacillin/tazobactam (–2.67; 95% CI –4.61 to –0.72) for comparison of the ASP intervention with other antibiotics that could also be affected. When we compared carbapenem antibiotic consumption with the prevalence of bacterial resistance for *Klebsiella pneumoniae* there was a positive association.

We extracted data regarding antibiotic resistance that our institution sent to the Antimicrobial Resistance Surveillance Network (REDNARBEC) regarding carbapenems, showing the following results. Resistance of *K. pneumoniae* to imipenem increased from 6% in 2010 to 40% in 2016 and 49% in 2017, while for meropenem it was, respectively, 4% (2010), 46% (2016) and 43% (2017).

4. Discussion

Although there was a punctual variation in 2015, global antibiotic consumption was stable in Ecuador's leading tertiary hospital during the study period, with β-lactams (J01C–JO1D) accounting for 60% of the total prescriptions. In absolute terms, the greater consumption was in ICU settings, where β-lactams (J01C–J01D) occupied the first place with 74% of the total consumption. When we stratified according to clinical settings, surgical patients showed a similar antibiotic consumption to the ICU, and both were higher than the clinical setting. The difference was also regarding the types of antibiotic consumed, but with no difference regarding carbapenems. The ASP played a significant role in reducing imipenem consumption and it appears to have affected other antibiotics as well.

4.1. Measuring antibiotic consumption

To establish an ASP, we employed antibiotic measures such as the WHO's ATC/DDD and Days of Therapy (DOT) [4]. Balancing advantages and setbacks of each method, we chose DDDs for being the most adopted and that could guarantee external validity to our findings [1,12,13]. Although there is discussion regarding the ideal method for measuring antibiotic consumption, using one is better than having none. Knowing the most used antibiotics in specific clinical scenarios can help healthcare managers guide ASPs, which our data corroborates along with others [14,15].

Although DDD is a standardised methodology to compare antibiotic consumption across many healthcare settings, some authors argue that the DDD format overestimates correct prescription practice by 40%, especially in the ICU. Therefore, they combined with other reference units such as Days of Therapy (DOT) and Prescribed Daily Dose (PDD). The WHO also released the 2019 WHO AWaRe Classification Database, a new classification system of antimicrobials based on their pharmacological classes to support countries for antibiotic monitoring and to implement rational use policies [16].

When we evaluated this dimension of our ASP for carbapenems, we observed a significant reduction for imipenem, without affecting meropenem consumption in a significant way, although there was a trend to increased use of the latter. One feature of the ASP is the undesired effect of 'squeezing the balloon', where restriction of a selected antibiotic will increase consumption of another of the same class or another class with similar spectrum of coverage. This seems not to be the case, especially when we observe the significant reductions for ceftriaxone and piperacillin/tazobactam. It seems that the ASP educational aspect had a positive influence on the consumption of other antibiotics, and the small in-

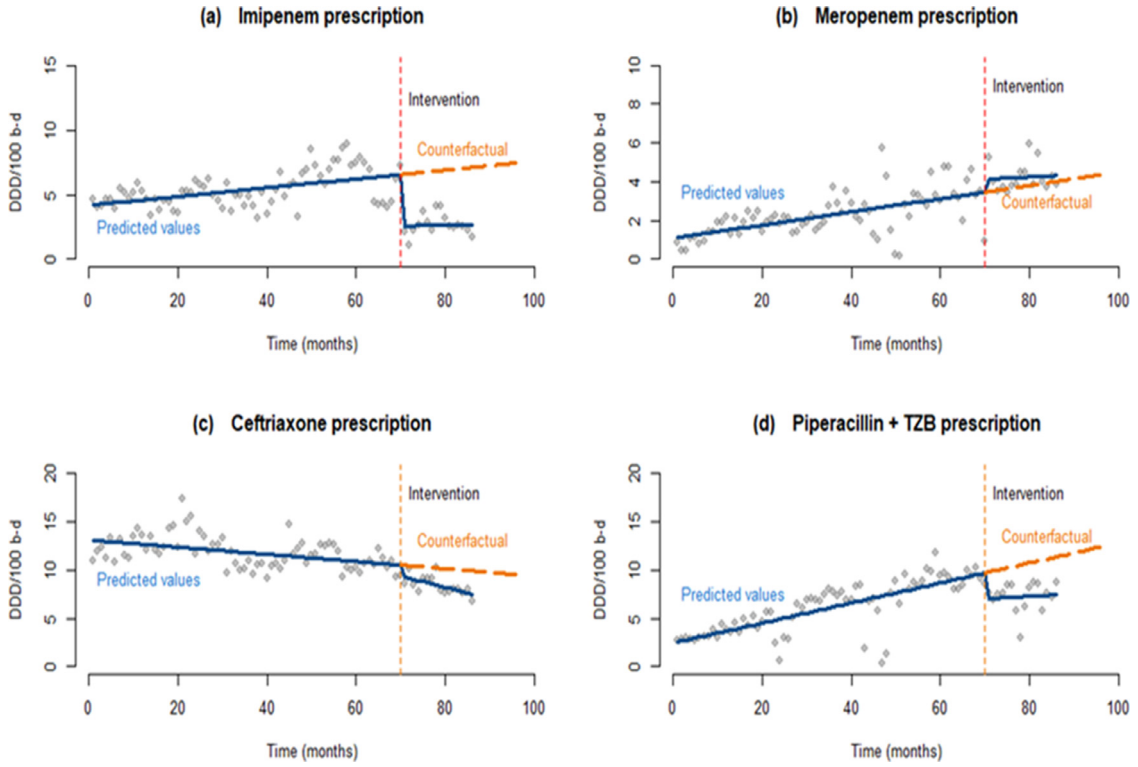


Fig. 2. Interrupted time series analysis of the effect of the antibiotic stewardship programme intervention on consumption of (a) imipenem, (b) meropenem, (c) ceftriaxone and (d) piperacillin/tazobactam. DDD, defined daily doses; b-d, beds-days.

crease in meropenem use may be due to other factors. Actually, our clinicians were aware of the increased resistance of some microorganisms to imipenem but not to meropenem by the time of ASP implementation.

4.2. Antibiotic resistance

Antibiotic resistance prevalence and clinical outcomes are two other dimensions proposed to evaluate ASPs [5]. These two dimensions also have some methods proposed for implementation and have some advantages and setbacks. Among the setbacks are the lack of randomised controlled studies, difficulties in gathering and systematically feeding internal and external regulatory agencies, and lack of standardised measures. Furthermore, mortality, length of stay and cure are the principal clinical outcomes measured incipiently, and many biases can influence the results, limiting comparison with other settings.

These three dimensions—consumption, antibiotic resistance and clinical outcomes—should be included when planning an ASP. Furthermore, one should acknowledge that besides the intervention's desired effect, one should be prepared to capture undesired effects and unexpected positive and negative occurrences [4]. Finally, antibiotic resistance appears to be a significant problem in LMICs, and specifically, dedicated guidelines are available to guide ASP implementation in these settings [2].

We evaluated our institution's ASP using the first two dimensions, namely consumption and antibiotic resistance. Regarding the first dimension, as stated, our findings are comparable with other institutions and can easily be included in our EHR for continuous follow-up [17,18].

Another finding was the association between increased carbapenem consumption and *K. pneumoniae* resistance prevalence. Although our data cannot establish a causal relationship, other studies in the literature support this finding. Our data showed an alarming increase in the resistance to *K. pneumoniae* and this is probably due to known factors such as selection pressure. Our institution should keep tracking antibiotic resistance, sending data to internal and external regulatory agencies, and correlating it with the other two ASP dimensions.

4.3. Limitations

We could not evaluate clinical outcomes in this retrospective study. This third dimension of ASP implementation will probably require a prospective follow-up, probably initiated with target diseases in the ICU, where antibiotic consumption and selective pressure assume a more critical role. We also did not classify our antibiotic lists following the WHO AWaRe programme, which is undoubtedly an essential issue to include in our ASP since reserving antibiotics will probably assume a vital role soon [19]. Another limitation is that we did not have data regarding carbapenem resistance classified genotypically. Unfortunately, we only began sending multiresistant bacteria isolated in our hospital to the state reference microbiology laboratory (INSPI) in order to classify them genotypically in 2018.

In conclusion, our ASP reduced imipenem consumption and affected the consumption of other antibiotics, probably due to its educational aspect. The ASP played a significant role in reducing imipenem consumption and it seems to have affected the prescription of other antibiotics as well.

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None.

Competing interests

None declared.

Ethical approval

This study was approved by our institution's ethical committee.

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