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Short report

Use of parenteral antimicrobials in very small hospitals in inner Brazil: patterns, determinants, and opportunities for interventions in developing countries

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SUMMARY

Much of healthcare in developing countries takes place in small hospitals. Little is known about the use of antimicrobials in those settings. We studied the 60-day use of parenteral antimicrobials in 48 hospitals with up to 50 beds in inner Brazil. The overall use was 242.0 defined daily doses per 100 admissions, and broad-spectrum agents accounted for 26.8%. The existence of local guidelines, educational measures and restrictive policies for antimicrobial prescriptions, as well as infection control and microbiology resources, were significantly associated with lesser use. Those findings point to possible interventions aimed at preventing antimicrobial over-use in developing countries.

Introduction

The World Health Organization's Global Action Plan on Antimicrobial Resistance includes among its main objectives the 'optimization of the use of antimicrobial medicines in human and animal health' [1]. It is estimated that BRIC countries (Brazil, Russia, India, and China) and South Africa account for three-quarters of the global increase in antimicrobial consumption from year 2000 to 2010 [2]. Still, little is known about patterns of antimicrobial use in those countries — and even less in settings outside large teaching hospitals.

In Brazil, hospitals with up to 50 beds comprise nearly two-thirds of the 6712 hospitals presently registered in the national database of healthcare settings (CNES, http://cnes.datasus.gov.br). Most of those hospitals are located in small cities, and deliver low-to-medium complexity medical, surgical, obstetric, and paediatric care [3]. They may be sites for the emergence and/or dissemination of antimicrobial resistance. Therefore, it is necessary to measure the magnitude of antimicrobial use and to identify opportunities for interventions aimed at optimizing anti-infective therapy in those settings.

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Methods

An ecological study was conducted, based on administrative data from 48 very small hospitals (VSH) from inner São Paulo State, Brazil. Since definitions for 'small' or 'very small' hospitals differ from country to country (and even within countries), VSH were defined arbitrarily as acute-care hospitals with up to 50 beds for inpatients. Psychiatric and other long-term-care hospitals, as well as emergency rooms that occasionally admitted patients, were not included in the definition. Hospitals were randomly selected from the CNES database. We were especially interested in studying VSH located far from the greatest cities, so we excluded those from the two metropolitan areas in the State (São Paulo City, 20 million inhabitants; Campinas, three million) and coastal cities (two million inhabitants). The remaining area comprises 570 municipalities, which collectively harbour 15 million inhabitants. In 2015, there were 286 VSH in São Paulo State. The 48 hospitals in our study were selected out of 195 VSH that were eligible on the basis of our geographic criteria. Hospital visits for data collection were conducted from March 2015 to December 2016.

Demographic data were collected from the cities where VSH were located. São Paulo State is divided into 17 administrative regions for healthcare, and hospital transfers of patients generally take place within a region. We used the number of teaching hospitals in each administrative region harbouring the study VSH as a proxy measure of interaction with high-complexity settings.

Characterization of VSH included financial nature and patterns of health care delivered. Of special interest, we collected evidence of the presence of infection control and antimicrobial stewardship: infection control committee (ICC), infectious diseases medical doctors, guidelines for anti-infective therapy, training on antimicrobial use for clinicians, restrictive control of antimicrobial prescription, and a reference microbiology laboratory. In order to adjust for possible seasonal variations in antimicrobial use, the season in which data were obtained was recorded.

The use of parenteral antimicrobials was collected from hospital pharmacies' records for the two months previous to our visit to each hospital. The magnitude of use was expressed in defined daily doses (DDD) per 100 admissions. Broad-spectrum agents were defined according to the classification proposed by Stenehjem *et al.* [4]. The following agents or classes met that definition: aminoglycosides, fluoroquinolones, aztreonam, ceftazidime, cefepime, ceftaroline, vancomycin, piperacillin—tazobactam, carbapenems, polymyxins, linezolid, and daptomycin.

As well as describing overall antimicrobial use, the aim was also to investigate the heterogeneity of patterns of antimicrobial use among different hospitals. Briefly, we attempted to find out whether there was a relatively homogeneous pattern for antimicrobial prescription, or if there were great differences in the use of specific agents or classes. In order to assess this topic, cluster analysis was performed, based on euclidean distances of values for individual agents or classes and unweighted pair group method with arithmetic mean (UPGMA). A threshold of one standard deviation was used for cluster definition.

Predictors of the magnitude of antimicrobial use were assessed using univariate and multivariate models of negative binomial regression with log link. Statistical analyses were carried out in SPSS 20 (IBM, Armonk, NY, USA), NCSS 9 (LLC, Kaysville, UT, USA) and STATA 14 (Stata, College Station, TX, USA).

Results

The study VSH had a median of 30 beds (range: 6—50) and collectively admitted 7325 patients in the study period. Even though 81.3% of hospitals were private, 95.8% delivered healthcare to patients covered by the Unified Health System — Brazilian programme of universal access to healthcare. The cities in which they were located had populations ranging from 6000 to 660,000 inhabitants. The proportion of VSH delivering medical, surgical, obstetric, and paediatric care were 97.9%, 62.5%, 64.6%, and 72.9%, respectively.

The overall use of parenteral antimicrobials was 242.0 DDD per 100 admissions. Broad-spectrum agents comprised 26.8% of total use. Results for specific agents or classes are presented in Table I. Cephalosporins and fluoroquinolones stood out as the most intensively used.

Cluster analysis identified 15 clearly distinct patterns of antimicrobial use. Briefly, there were three similarity clusters, comprising 31, three and two hospitals, respectively. The remaining 12 VSH presented unique patterns. This points to heterogeneity in prescribing patterns among hospitals.

Results from the analysis of factors associated with the magnitude of parenteral antimicrobial use were as follows. In univariate regression models, admission of medical patients and data collected in cold seasons (April to September) were significantly associated with greater antimicrobial use. On the other hand, the presence of an ICC active for at least five years, antimicrobial guidelines, training in anti-infective therapy, and restrictive policies were predictors of lesser use. When the outcome was switched to broad-spectrum agents, results were similar to the previous analysis for two predictors: admission of medical patients and training for clinicians.

Table II presents the effect of infection control and antimicrobial stewardship on the magnitude of use of parenteral antimicrobials in multivariate models adjusted for demographic variables and hospital characteristics. Besides factors previously identified, the presence of microbiology laboratory and ICC active for five years were associated with less use of overall and broad-spectrum agents, respectively.

Discussion

Presently, both the USA and Europe are facing the challenge of monitoring antimicrobial use in hospitals [5,6]. Metrics can provide useful information to direct interventions for optimizing prescriptions and, ultimately, prevent the emergence and spread of resistant organisms [7]. In order to achieve these goals, the available data must be comprehensive enough to include hospitals of different sizes and patterns of healthcare delivery. It has been previously noticed that, even in developed countries, there are scarce data on antimicrobial use in small hospitals [4].

Our results point to extensive use of antimicrobials in VSH in Brazil, including broad-spectrum agents. Roughly comparing, if we use the mean time of admission for patients in VSH in Brazil (which is 4.5 days, according to governmental data available at

Table I
Use of specific antimicrobial agents or classes among 48 very small hospitals in inner São Paulo State, Brazil

Antimicrobials	Pooled rate	Minimum	Percentiles					Maximum
			10	25	50 (median)	75	90	
Ceftriaxone	97.97	0.00	48.79	64.46	112.02	168.27	266.73	414.68
Fluoroquinolones[a]	42.58	0.00	0.00	7.24	23.21	45.45	69.87	183.08
Cephalosporins, first generation	34.17	0.00	0.00	7.16	21.86	47.58	74.04	213.46
Penicillins	12.82	0.00	0.00	0.00	0.00	0.00	3.37	605.18
Clindamycin	12.70	0.00	0.00	0.00	5.40	18.76	31.59	142.31
Metronidazole	8.69	0.00	0.00	0.00	2.42	15.11	27.04	52.91
Aminoglycosides[a]	8.51	0.00	0.00	0.00	1.92	9.41	18.08	203.19
Cefepime[a]	7.84	0.00	0.00	0.00	0.00	0.00	12.01	114.68
AmoxClav	6.62	0.00	0.00	0.00	0.00	0.00	10.16	113.47
Carbapenems[a]	2.78	0.00	0.00	0.00	0.00	0.00	4.17	19.14
Vancomycin[a]	2.20	0.00	0.00	0.00	0.00	0.00	2.38	18.10
Macrolides	2.01	0.00	0.00	0.00	0.00	0.00	1.24	22.97
Cloramphenicol	1.56	0.00	0.00	0.00	0.00	0.00	1.43	39.48
PipTaz[a]	0.88	0.00	0.00	0.00	0.00	0.00	0.00	30.43
SmxTmp	0.71	0.00	0.00	0.00	0.00	0.22	1.34	23.15

AmoxClav, amoxicillin–clavulanate; PipTaz, piperacillin–tazobactam; SmxTmp, sulfamethoxazole–trimethoprim.
Data are presented as number of defined daily doses (DDD) per 100 admissions. Antimicrobial agents or classes are presented in descending order of pooled rates. The distribution of individual hospital rates in percentiles discloses the great heterogeneity in patterns of antimicrobial use.
Cefotaxime, ceftazidime, ceftraroline, polymyxins, teicoplanin, daptomycin, linezolid were not used in the study hospitals. There was also no use of parenteral antifungals or antivirals.
[a] Broad-spectrum agents. All other agents or classes are termed 'narrow spectrum' in the classification proposed by Stenehjem *et al.* [4].

http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/sxuf.def), 242.0 DDD per 100 admissions may be converted to an estimated 537.8 DDD per 1000 patient-days. DDD are indirect estimates of days-of-therapy (DOT). Therefore, in spite of some differences in methods for calculation of metrics, those values are higher than those reported by Stehnejem *et al.* (436 DOT per 1000 patient-days) [4].

Patterns of use varied widely among hospitals, as noticed both in the percentile distribution of individual rates (Table I) and in the cluster analysis.

Table II
Effect of infection control and antimicrobial stewardship items on the use of total parenteral antimicrobials and broad-spectrum agents

Factors	Crude RR	Adjusted RR (1)	Adjusted RR (2)	Adjusted RR (3)
Overall use				
ICC	0.81 (0.56–1.17)	0.79 (0.55–1.15)	0.85 (0.60–1.22)	0.87 (0.64–1.20)
ICC, 5 years[a]	0.64 (0.47–0.87)*	0.72 (0.51–1.01)	0.59 (0.45–0.79)*	0.69 (0.52–0.91)*
ID specialist	1.02 (0.46–1.86)	0.91 (0.52–1.59)	2.13 (1.07–4.21)*	1.60 (0.86–3.00)
Local guidelines	0.63 (0.46–0.88)*	0.62 (0.45–0.86)*	0.69 (0.50–0.94)*	0.63 (0.47–0.85)*
Training for doctors	0.50 (0.38–0.67)*	0.51 (0.40–0.66)*	0.55 (0.41–0.74)*	0.56 (0.44–0.72)*
Restrictive control	0.64 (0.47–0.87)*	0.60 (0.45–0.80)*	0.72 (0.53–0.98)*	0.67 (0.55–0.87)*
Microbiology	0.75 (0.41–1.35)	0.63 (0.37–1.08)	0.76 (0.44–1.30)	0.55 (0.35–0.86)*
Broad spectrum				
ICC	0.94 (0.46–1.91)	0.70 (0.36–1.62)	0.80 (0.38–1.67)	0.71 (0.32–1.54)
ICC, 5 years[a]	0.63 (0.34–1.19)	0.48 (0.20–1.15)	0.48 (0.26–0.86)*	0.40 (0.19–0.83)*
ID specialist	0.92 (0.29–2.90)	0.83 (0.26–2.66)	1.84 (0.46–7.43)	1.25 (0.91–1.38)
Local guidelines	0.78 (0.40–1.52)	0.71 (0.32–1.56)	0.67 (0.35–1.30)	0.64 (0.31–1.34)
Training for doctors	0.51 (0.27–0.96)*	0.42 (0.22–0.83)*	0.50 (0.27–0.94)*	0.44 (0.22–0.89)*
Restrictive control	0.94 (0.50–1.78)	0.67 (0.32–1.38)	1.04 (0.54–2.02)	0.88 (0.44–1.74)
Microbiology	0.92 (0.29–2.89)	0.70 (0.21–2.36)	0.78 (0.28–2.17)	0.62 (0.22–1.70)

RR, rate ratio; ICC, infection control committee; ID, infectious diseases.
Data were collected in administrative files and archives of the ICC. The adjustments were made for: (1) demographic and environmental data, including: population, human development index and Gini index of inequalities in income for cities where hospitals were located; number of teaching hospitals in the administrative region where the hospitals were located; seasons when data were collected (cold, April to September versus warm, October to March); (2) hospital characteristics, including: financial nature, delivering care to the Unified Health System, admission of medical, surgical, obstetric and/or paediatric patients; (3) all variables listed in (1) and (2).
*$P < 0.05$.
[a] ICC active for at least five years.

This poses a challenge for implementing antimicrobial stewardship programmes. However, our data also suggest that the presence of ICC active for five years or more may significantly decrease antimicrobial use. According to regulations of the Ministry of Health, ICCs in Brazil are expected to perform surveillance, prevention, and control of healthcare-associated infections, and also to run antimicrobial stewardship programmes. Coherently, we found that stewardship items such as local guidelines, training for doctors and restrictive policies for prescriptions were also associated with less use of antimicrobials. It is worth noting that, in the past decades, several efforts have been made in Brazil in order to implement infection control in hospitals [8]. Even though results for VSH are still poor, governmental policies may have favourably impacted our findings.[9].

There are several limitations of our study. We did not have access to patient-level data. Therefore, our metrics were based on DDD, instead of DOT — the metrics recommended in the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America guidelines [10].

We also collected information for a very short span of time. The rationale for this approach was that recent data could be more precise and reliable. Nevertheless, wide differences in size and number of admissions in the study period account for some extreme individual values in our results.

However, there are also strengths in our study. In the face of absence of information systems of antimicrobial use, data were collected on site, during visits to the study hospitals. Our analysis was based on negative binomial regression models that compared aggregate rates while correcting for over-dispersion in outcome values.

In conclusion, we found that having an ICC active for at least five years and institution of antimicrobial stewardship items may reduce the use of antimicrobials in VSH. Previous evidence on the effectiveness of antimicrobial stewardship stems mainly from studies conducted in large hospitals from developed countries. Our results point to opportunities for preventing over-use of antimicrobials in small hospitals, not only in those countries, but also in limited-resource settings and developing countries.

Conflict of interest statement
None declared.

Funding sources
None.

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