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Brief Original Article

Antimicrobial resistance and antibiotic consumption in a third level pediatric hospital in Mexico City

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Abstract
Introduction: The increasing resistance to antibiotics is a public health problem and an imminent therapeutic challenge in hospitals. In this report we aimed to analyze the relationship between antimicrobial resistance and antibiotic consumption in a third-level pediatric hospital.
Methodology: A cross-sectional analysis was conducted using the information from the microbiology and pharmacy databases of the Pediatric Hospital "Doctor Silvestre Frenk Freund", during the period 2015-2018. Prevalence of antimicrobial resistance by microorganisms and dispensed grams of selected antibiotics were calculated annually. Antibiotic resistance trend over the time was evaluated using the Chi-square trends test and to assess the correlation between the dispensed grams of antibiotics with their antimicrobial resistance prevalence, we calculated the Pearson's coefficient (r).
Results: A total of 4,327 isolated bacterial samples were analyzed (56.5% Gram-positive and 44.5% Gram-negative). Most frequently isolated microorganisms were coagulase-negative staphylococci (CoNS), *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *S. aureus*
We found a significant increase in resistance to clindamycin and oxacillin for CoNS and significant decrease in nitrofurantoin and amikacin resistance for *E. coli* and *K. pneumoniae*. We observed a strong positive and statistically significant correlation between amikacin resistance prevalence and amikacin dispensed grams for *P. aeruginosa* ($r = 0.95$, $p = 0.05$).
Conclusions: The antibiotic resistance profile showed by our study highlights the need of an appropriate antibiotic control use in the Hospital setting.

Key words: Antimicrobial resistance; antibiotic consumption; Health Care-Associated Infections.

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Introduction
The transmission of multidrug-resistant pathogens in hospitals, such as *Acinetobacter baumannii* carbapenem-resistant, *Pseudomonas aeruginosa* carbapenem-resistant and *Enterobacteriacea* carbapenem-resistant, ESBL-producing, is considered as an important public health threat [1]. The knowledge on local microbiology, the resistance patterns and their relationship with usage metrics of antibiotics are the principal measures considered by the "antimicrobial stewardship" strategy which tries to reduce multidrug-resistant microorganism transmission among hospitals [2]. In this study we aimed to identify the trends in antibiotic resistance obtained by isolated microorganisms in clinical samples taken during hospitalization and the relationship between the use of antibiotics and their resistance in the Third-level Pediatric Hospital "Doctor Silvestre Frenk Freund", located in Mexico City, which has an average of 6,700 hospitalizations per year.

Methodology
A cross-sectional analysis was conducted using the information from the Pediatric Hospital microbiology database. First isolated bacterial species from blood, urine, normally sterile body fluids and aspiration puncture cultures were included. The samples corresponded to in-hospital patients from the period 2015-2018. Microorganism identification and antimicrobial susceptibility were carried out using the broth microdilution technique through Vitek 2 automated system (BioMérieux, Lyon, France). Minimum inhibitory concentrations (MIC) were interpreted using the 2018 version CLSI criteria [3].

Annual prevalence of antimicrobial resistance by microorganisms was calculated with their corresponding 95% Confidence Interval (CI) and Chi-square trends were used to assess their behavior over time. Dispensed grams of selected antibiotics were calculated annually, using the information from the pharmacy database and to assess the correlation between those grams and the antimicrobial resistance prevalence; the Pearson's coefficient (r) was calculated and P values < 0.05 were considered statistically significant. WHONET Desktop 2019, IBM SPSS Statistics version 25 (IBM Inc.) and Tableau Desktop ® 2019 (Tableau® Software Inc.) were used to carried out the statistical analysis. The research was approved by the Ethical Committee Number 3603 of the Mexican Institute of Social Security with registration number R-2020-3603-013. All methods were performed in accordance with ethical standards and regulations from the institutional research committees and national laws and with the 1964 Helsinki declaration and its later amendments. Given that this study was based on the use of available databases with no personal identifiers, not formal informed consent was required.

Table 1. Antimicrobial resistance prevalence.

Microorganism/antibiotic	Antimicrobial resistance (%)					Slope	P-value
	2015	2016	2017	2018	Total		
Staphylococci							
Coagulase-negative staphylococci							
Ciprofloxacin	63.0	54.7	57.7	55.0	57.8	0.02	0.140
Clindamycin	72.0	70.2	76.6	70.7	72.3	0.04	0.008*
Gentamicin	55.5	52.0	51.2	44.0	50.7	0.02	0.266
Linezolid	0.0	4.1	0.0	0.0	1.0	0.00	0.385
Oxacillin	86.5	88.2	89.2	94.8	89.7	0.10	<0.001*
Rifampin	12.3	14.7	19.5	8.9	13.6	0.00	0.633
Trimethoprim / Sulfamethoxazole	64.0	55.0	75.0	53.4	58.1	0.02	0.197
Vancomycin	1.4	8.2	13.7	4.2	6.5	0.01	0.144
S. aureus							
Ciprofloxacin	NA	NA	17.9	17.7	17.5	NA	0.987
Clindamycin	NA	NA	36.8	38.7	37.2	NA	0.834
Gentamicin	NA	NA	3.6	3.2	4.1	NA	0.917
Linezolid	NA	NA	0.0	0.0	0.0	NA	NA
Oxacillin	NA	NA	21.4	58.1	40.0	NA	<0.001*
Rifampin	NA	NA	3.5	1.6	2.5	NA	0.510
Trimethoprim/Sulfamethoxazole	NA	NA	5.3	6.5	5.8	NA	0.783
Vancomycin	NA	NA	0.0	0.0	0.0	NA	NA
Enterobacteria							
E. coli							
Amikacin	4.2	5.6	2.2	0.8	3.1	-0.01	0.046*
Cefazolin	59.3	64.8	60.4	64.6	62.3	0.01	0.568
Ceftriaxone	56.8	59.7	59.7	61.5	59.5	0.01	0.471
Ciprofloxacin	59.2	56.1	60.4	57.7	58.4	0.00	0.998
Meropenem	0.8	2.4	4.3	1.5	2.2	0.00	0.543
Nitrofurantoin	5.0	3.9	2.2	0.0	2.7	-0.02	0.010*
Piperacillin/Tazobactam	12.5	29.2	24.1	25.2	22.8	0.03	0.054
Tigecycline	0.0	0.0	0.0	0.0	0.0	0.00	NA
Trimethoprim/Sulfamethoxazole	68.9	58.5	65.7	63.8	64.2	-0.01	0.699
K. pneumoniae							
Amikacin	3.6	1.2	6.4	0.0	3.1	0.00	0.615
Cefazolin	73.8	67.5	65.7	73.3	69.7	-0.01	0.804
Ceftriaxone	74.7	63.5	65.4	68.3	67.8	-0.02	0.437
Ciprofloxacin	14.3	13.1	18.5	22.2	17.1	0.03	0.113
Meropenem	0.0	1.2	1.0	0.0	0.6	0.00	0.978
Nitrofurantoin	13.4	9.4	10.1	8.6	10.4	-0.01	0.368
Piperacillin/Tazobactam	13.1	13.4	14.3	12.0	13.3	0.00	0.914
Tigecycline	4.8	4.8	0.0	0.0	2.4	-0.02	0.010*
Trimethoprim / Sulfamethoxazole	66.7	56.1	59.3	69.1	62.5	0.01	0.710

Table 1 (continued). Antimicrobial resistance prevalence.

Microorganism/antibiotic	Antimicrobial resistance (%)					Slope	P-value
	2015	2016	2017	2018	Total		
Enterobacter spp							
Amikacin	12.0	3.1	4.1	3.7	5.3	-0.02	0.249
Ceftriaxone	21.7	14.7	30.6	32.1	25.4	0.06	0.134
Ciprofloxacin	8.0	5.7	4.1	3.7	5.1	-0.01	0.457
Meropenem	12.0	2.9	7.5	10.7	7.9	0.00	0.867
Nitrofurantoin	12.0	3.1	0.0	0.0	3.0	-0.05	0.002*
Piperacillin/Tazobactam	17.4	9.1	12.5	11.1	12.2	-0.01	0.696
Tigecycline	4.0	0.0	0.0	0.0	0.8	-0.01	0.137
Trimethoprim/Sulfamethoxazole	32.0	12.1	12.2	25.9	18.7	-0.02	0.622
Non-fermenting microorganisms							
A. baumannii							
Cefepime	38.5	60.0	18.2	57.9	47.6	0.02	0.555
Ceftriaxone	38.5	64.1	20.0	57.9	49.6	0.02	0.601
Ciprofloxacin	34.6	57.5	15.0	43.8	41.5	-0.01	0.726
Gentamicin	15.4	50.0	5.0	31.3	29.7	0.00	0.971
Meropenem	NA	100.0	0.0	55.3	54.7	NA	NA
Piperacillin/Tazobactam	25.0	60.0	0.0	50.0	49.2	0.02	0.760
Trimethoprim/Sulfamethoxazole	38.5	64.1	15.0	46.9	45.3	-0.02	0.585
P. aeruginosa							
Amikacin	16.7	14.3	12.4	6.4	12.3	-0.03	0.032*
Cefepime	11.3	12.5	11.3	7.4	10.4	-0.01	0.372
Ciprofloxacin	10.3	11.3	14.3	11.7	12.0	0.01	0.620
Gentamicin	16.7	14.1	11.5	11.7	13.4	-0.02	0.261
Meropenem	16.7	17.1	20.0	12.6	16.5	-0.01	0.576
Piperacillin/Tazobactam	14.7	16.4	2.9	2.6	9.4	-0.05	0.001*

Data are presented as percentage. Slope and P-value were calculated with the Chi-square trend test. *P<0.05; NA: not available.

Figure 1. Antimicrobial resistance prevalence by microorganism.

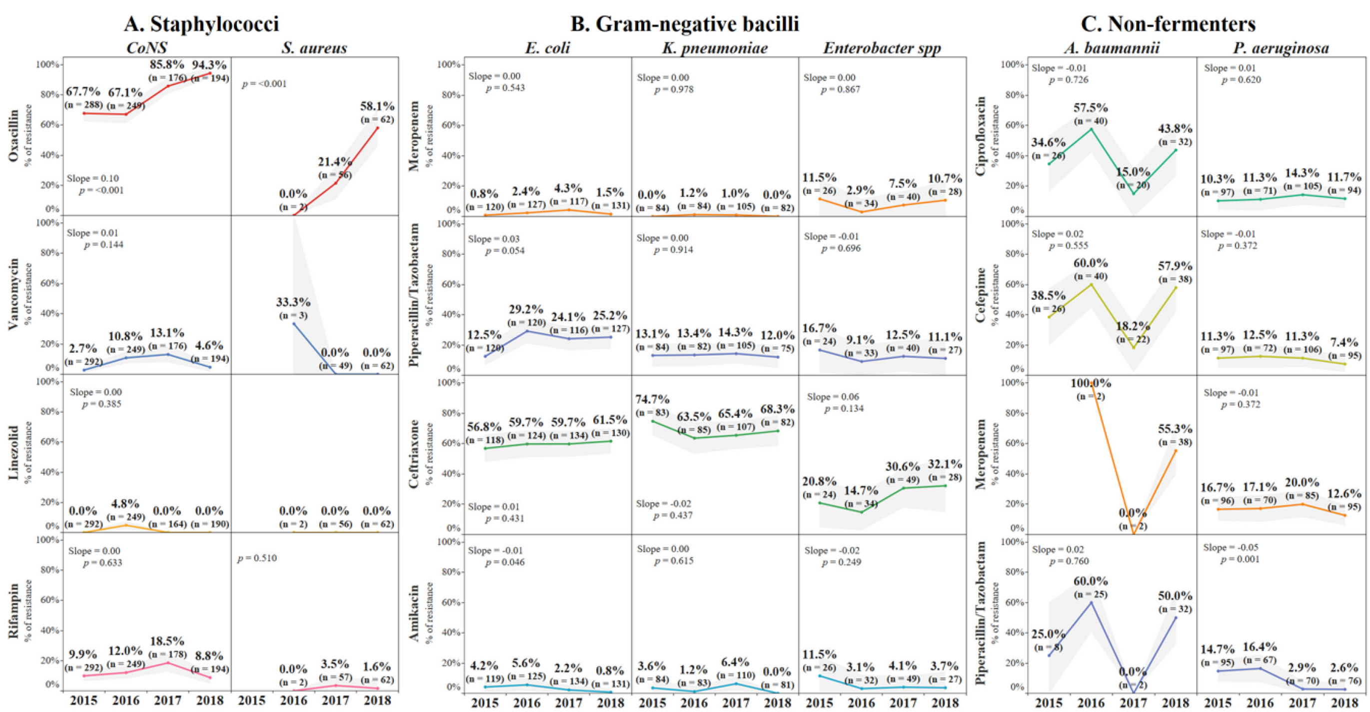
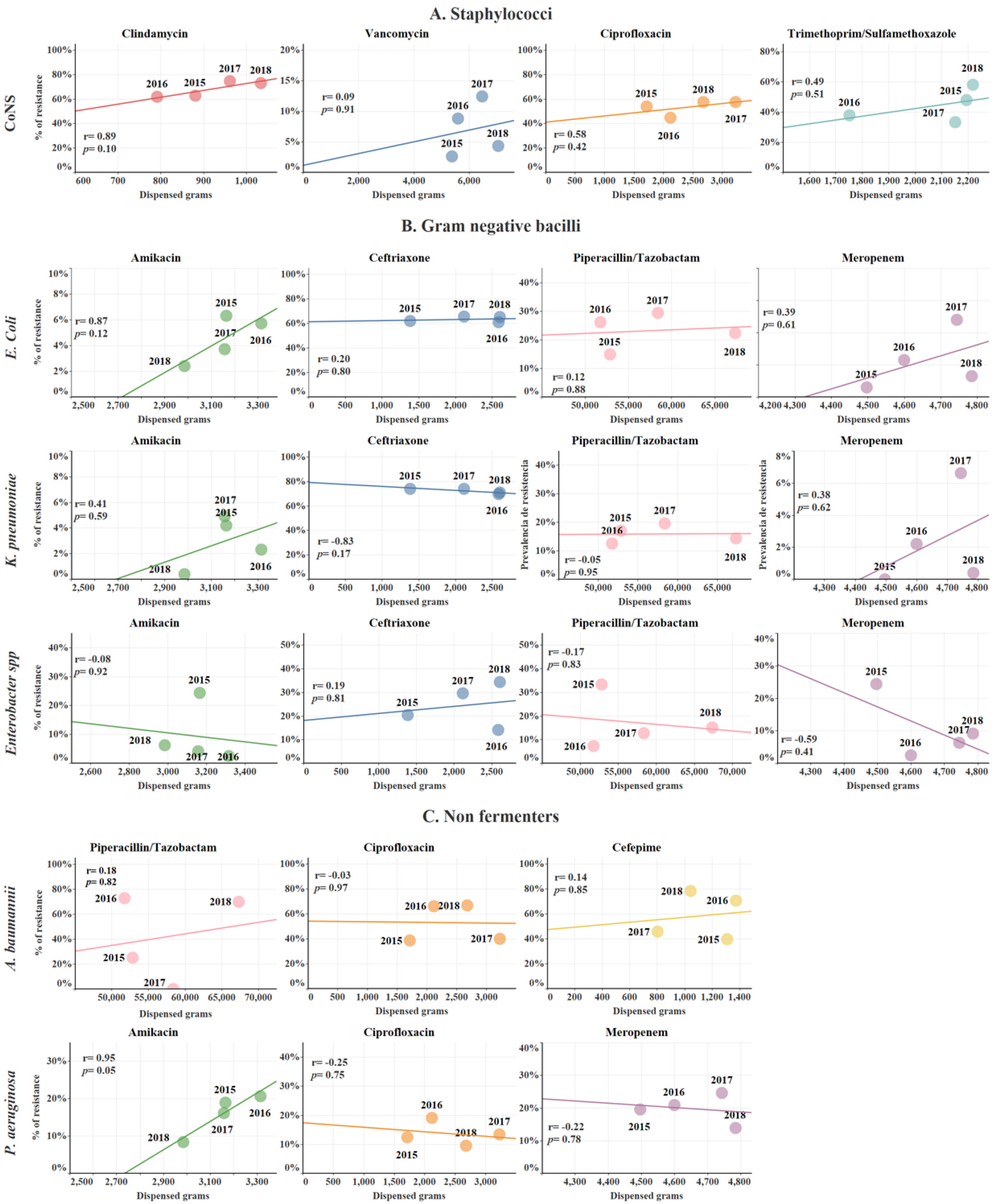


Figure 2. Correlation between dispensed grams of selected antibiotics and antimicrobial resistance.



Results

A total of 4,327 isolated bacterial species were analyzed (56.5% Gram-positive and 44.5% Gram-negative). Most frequently isolated microorganism were coagulase-negative staphylococci (CoNS), *E. coli*, *K. pneumoniae*, *P. aeruginosa* con and *S. aureus* with 25.4%, 13.0%, 9.8%, 9.7% and 5.0% of the total, respectively.

Antimicrobial resistance prevalence

Staphylococci group, including CoNS and *S. aureus*, showed high resistance prevalence to Oxacilin and Clindamycin, while third generation cephalosporins, ciprofloxaxin and Trimethoprim/Sulfamethoxazole had the highest resistance prevalence for *Enterobacteria* group and *A. baumannii* (Table 1).

In the trend analysis of antimicrobial resistance over the time, we found a significant increase in resistance to clindamycin and oxacillin for CoNS and significant decrease in nitrofurantoin and amikacin resistance for *E. coli* and *K. pneumoniae* (Figure 1).

Correlation between dispensed grams of selected antibiotics and antimicrobial resistance

We observed a strong positive and statistically significant correlation between amikacin resistance prevalence and amikacin dispensed grams for *P. aeruginosa* in the Pediatric Hospital ($r = 0.95$, $p = 0.05$).

We also observed strong positive correlations between clindamycin ($r = 0.89$, $p = 0.1$), amikacin ($r = 0.87$, $p = 0.1$) and ciprofloxacin ($r = 0.81$, $p = 0.2$) resistance and consumption for CoNS, *E. coli* and *K. pneumoniae,* respectively. Negative strong correlations between resistance and consumption were found in nitrofurantoin ($r = -0.84$, $p = 0.1$), ceftriaxone ($r = -0.83$, $p = 0.2$), ciprofloxacin ($r = -0.84$, $p = 0.2$) and piperacillin / tazobactam ($r = -086$, $p = 0.1$) for *E. coli*, *K. pneumoniae*, *Enterobacter* and *P. aeruginosa,* respectively (Figure 2).

Discussion

As previous studies related to microbiology did, we also found that the most frequently isolated microorganisms were Gram-negative, mainly *E. coli*, *K. pneumoniae* and *P. aeruginosa* [4–7].

Similar to previous reports in Mexico, our study found an increasing tendency for MRSA in *S. aureus* [8,9], a high resistance for third generation cephalosporins in *E. coli* and *K. pneumoniae* [10,11], a multiple simultaneous antibiotic resistance pattern for *A. baumannii* [5,6,12] and an increasing resistance for carbapenems in *P. aeruginosa* [8]. However, carbapenems trends were stable for the main Gram-negative bacilli (*E. coli* and *K. pneumoniae*), which could be explained by the strict antibiotic use policy in this Hospital.

Among the limitations of this study, we can mention that all the microorganisms reported in the cultures (including colonization and contamination) were analyzed, so the found patterns could be different for the microorganisms and the main HAIs. Another important limitation was that the dispensed grams of antibiotics provided by the pharmacy may not faithfully reflect the consumption of antibiotics at the pediatric population, where the dose depends mainly on the patient's weight, the site of infection and the antibiotic therapy duration. Also, due to technical problems, no complete information was recorded for several antibiotics prescribed for *S. aureus* in 2015 and 2016, so the results are incomplete for this microorganism.

Despite the above mentioned limitations our study found an increase in oxacillin resistance in Staphylococci and a decrease in aminoglycosides resistance in Gram-negative microorganisms and also a correlation between amikacin resistance prevalence and amikacin dispensed grams for *P. aeruginosa*.

Conclusion

Our results highlight the need of an appropriate antibiotic use in the Hospital setting, in order to limit the increase of antimicrobial resistance.

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Authors' Contributions

RAF, JGVR and RJRR conceived the study. DARR carried out statistical analyses, interpreted the data and drafted the manuscript. IJAM y RCO contributed to the analysis plan and reviewed the manuscript.

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