

Uso de antibióticos e associação com resistência bacteriana em um hospital no Sul do Brasil

Antibiotic use and association with bacterial resistance in a hospital in Southern Brazil

Uso de antibióticos y asociación con resistencia bacteriana en un hospital del Sur de Brasil

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Resumo

Introdução. O aumento da produção de novas drogas emerge paralelamente com a adaptação bacteriana a condições adversas. Existem diversos fatores que tem sido apontados como causa desta condição tais como: globalização, uso abusivo de antibióticos, e a prescrição arbitrária destas drogas. Com isso, o objetivo do estudo foi avaliar o uso de antimicrobianos com a antibiótico-resistência em 2012 e 2013 em um Hospital Universitário do Sul do Brasil. **Material e métodos.** Este estudo foi realizado no Hospital Universitário Dr. Miguel Riet Correa Jr. em Rio Grande/RS, Brasil. Os dados foram coletados entre Janeiro de 2012 e Dezembro de 2013, na clínica médica e duas unidades de tratamento intensivo. **Resultados.** Observou-se 385 e 464 casos de infecções bacterianas, durante os anos de 2012 e 2013, respectivamente. *Acinetobacter baumannii*, *Escherichia coli* e *Klebsiella pneumoniae* foram as espécies mais prevalentes. O consumo total de antibióticos no Hospital Universitário (HU-FURG), neste período, foi de 3.865 unidades/doses, sendo 1.995 unidades/dose em 2012 e 1.870 unidades/dose no ano de 2013. A relação entre as taxas dos principais patógenos resistentes isolados e o consumo anual do antibioticoa correspondentea (carbapenêmicos, cefalosporinas, sulfonamidas e outros β -lactâmicos) foi observada; entretanto, não mostrou associação significativa entre o aumento da resistência e o consumo. **Conclusão.** Este estudo revela a necessidade de disseminação e retorno destes dados para os clínicos e tomadores de decisão no hospital, pois pode ser crucial o melhoramento de políticas na prescrição de antibiotioc e na implementação de um crontrôle eficaz das infecções..

Palavras-chave: Antimicrobianos; Bacteria; Infecção nosocomial.

Abstract

Introduction. The increased production of new drugs is parallel with the bacterial adaptation to adverse conditions. There are several factors that have been pointed out as the cause of this, such as: globalization; the abusive use of antibiotics; and the arbitrary prescription of these drugs. Therefore, the objective of the present study was to evaluate antimicrobial usage with antibiotic resistance in 2012 and 2013 at a university hospital in Southern Brazil. **Material and Methods.** This study was performed at the University Hospital Dr. Miguel Riet Correa Jr. in Rio Grande/RS, Brazil. The data were collected between January 2012 and December 2013, using data from the medical clinic and two intensive care units. **Results.** Were observed, 385 and 464 cases of bacterial infections, during the years of 2012 and 2013, respectively. *Acinetobacter baumannii*, *Escherichia coli* and *Klebsiella pneumoniae* were the most prevalent species. The total antibiotic consumption in the University Hospital (HU-FURG) in

this period was 3.865 units/dose, with 1.995 units/dose in the year 2012 and 1.870 units/dose in the year 2013. Relationships between the rates of main resistant pathogens isolated and the annual consumption of the corresponding antibiotic (carbapenems, cephalosporins, sulfonamides and other β -lactams) were observed; however, they did not show significant positive associations in increased resistance associated with increased consumption. Conclusion. This study reveals the need for the dissemination and feedback of these data to clinicians and decision-makers at the hospital, as it may be crucial to improve policies on prescribing antibiotics and to implement effective infection control.

Keywords: Antimicrobial; Bacterial; Nosocomial infection.

Resumen

Introducción. El aumento en la producción de nuevos medicamentos surge en paralelo con la adaptación bacteriana a las condiciones adversas. Hay varios factores que se han identificado como la causa de esta afección, como: globalización, abuso de antibióticos y prescripción arbitraria de estos medicamentos. Por lo tanto, el objetivo del presente estudio fue evaluar el uso de antimicrobianos con resistencia a los antibióticos en 2012 y 2013 en un hospital universitario en el Sur de Brasil. Material y métodos. Este estudio se realizó en el Hospital Universitario Dr. Miguel Riet Correa Jr. en Rio Grande / RS, Brasil. Los datos se recopilaron entre enero de 2012 y diciembre de 2013, en la clínica médica y dos unidades de cuidados intensivos. Resultados. Se observaron 385 y 464 casos de infecciones bacterianas durante los años 2012 y 2013, respectivamente. *Acinetobacter baumannii*, *Escherichia coli* y *Klebsiella pneumoniae* fueron las especies más prevalentes. El consumo total de antibióticos en el Hospital Universitario (HU-FURG), en este período, fue de 3,865 unidades / dosis, siendo 1,995 unidades / dosis en 2012 y 1,870 unidades / dosis en 2013. La relación entre las tasas de los principales patógenos resistentes aislado y se observó el consumo anual del antibiótico correspondiente (carbapenémicos, cefalosporinas, sulfonamidas y otras β -lactamas); Sin embargo, no hubo una asociación significativa entre el aumento de la resistencia y el consumo. Conclusión. Este estudio revela la necesidad de difundir y devolver estos datos a los médicos y tomadores de decisiones en el hospital, ya que puede ser crucial para mejorar las políticas en la prescripción de antibióticos y en la implementación de un control efectivo de infecciones.

Palabras clave: Antimicrobianos; Bacterias; Infección nosocomial.

1. Introduction

Throughout human history, microbial infections have been responsible for a range of endemic and epidemic diseases that have resulted in several consequences at the community level (Sengupta, Chattopadhyay, & Grossart, 2012). Subsequently, the modern era of antibiotics, with the discovery of penicillin in 1928, brought with it what we call the “Trojan horse”, or bacterial resistance (Gaynes, 2017).

The increased production of new drugs is parallel with the bacterial adaptation to adverse conditions, and the resistance is primarily the result of this exposure (Barriere, 2015; Spellberg, Bartlett, & Gilbert, 2013). The fact that distinguishes an antimicrobial from any other therapeutic product is the ability of the first to lose effectiveness over time, requiring the constant replacement of these through the discovery of new drugs (Luepke et al., 2013). According to the World Health Organization, antibiotic resistance is extremely widespread around the world in both high- and low-income countries. *Escherichia coli*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* are the most commonly reported resistant bacteria (WHO, 2018).

There are several factors that have been pointed out as the cause of bacterial resistance, such as: globalization, as a facilitator of transmission of pathogen resistance mechanisms across the world; the abusive or inappropriate use of antibiotics; the massive use of antimicrobials in agricultural animals; and the arbitrary prescription of these drugs (Hawkey, et al., 2015; Zowalaty, et al., 2016; Raevuori, et al., 2016; Helke, et al., 2016; Crichton, et al., 2018). It is important to note that the increase in antimicrobial resistance has generated a clear effect on the morbidity and mortality of patients, due to the reduction in therapeutic options and to extended and more expensive hospitalization periods, along with drastic consequences to the health system (Kalpoe, et al., 2012; Harris, et al., 2013; MacGowan, 2012). The stronger resistance of organisms to some antimicrobial agents is frequently associated with the heavy use of a few antimicrobials.

Taking this fact in view, this report aims to evaluate antimicrobial usage with antimicrobial resistance in 2012 and 2013 at a university hospital in Southern Brazil.

2. Methodology

The study is an exploratory research, conducted through a transversal and observational methodology. The quantitative data about bacterial infections were obtained

from patients attending in three sectors [medical clinic, general intensive care unit (ICU), and neonatal ICU] of the University Hospital Dr. Miguel Riet Correa Jr. (HU-FURG), located in Rio Grande, Rio Grande do Sul, between January 2012 and December 2013.

The bacterial identification and assessment of susceptibility to antimicrobials was performed by Phoenix system (Becton Dickson, Sparks, MD) in the Clinical Analysis Laboratory of HU-FURG. Data on quarterly antibiotic consumption, prophylactic or therapeutic, in each sector were evaluated, from 2012 to 2013 and were obtained from the Nosocomial Infection Control Committee of the hospital.

A Chi-square (χ^2) test was used to determine the relationship between antibiotic consumption and trends in resistance, at the 95% significance level ($p \leq 0.05$), by GraphPad Prism 5.0. Cluster Analysis was performed to evaluate the microbial profile by hospital sectors in the years of 2012 and 2013, considering the Euclidean distance between samples (SPSS 22.0 software).

This research followed Resolution 466/12 of Conselho Nacional de Saúde, which regulates research involving humans. The study was approved by the Ethical Committee of Federal University of Rio Grande (number 22/2014).

3. Results

During the study period, there were 385 and 464 cases of bacterial infections identified by Phoenix platform during the years of 2012 and 2013, respectively. According Table 1, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus* spp. (*Staphylococcus aureus*, *Staphylococcus haemolyticus*, *Staphylococcus capitis*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Staphylococcus saprophyticus*) were the most prevalent species in the period and sectors evaluated. It is important to note that *Staphylococcus* sp. is the most prevalent in the three sectors, because due to the lack of identification of each species, but of the genus as a whole. In addition, we observed that neonatal - ICU is the sector with the lowest number of infection cases in the two years evaluated, in contrast to medical clinical, which reaches 251 cases in 2013.

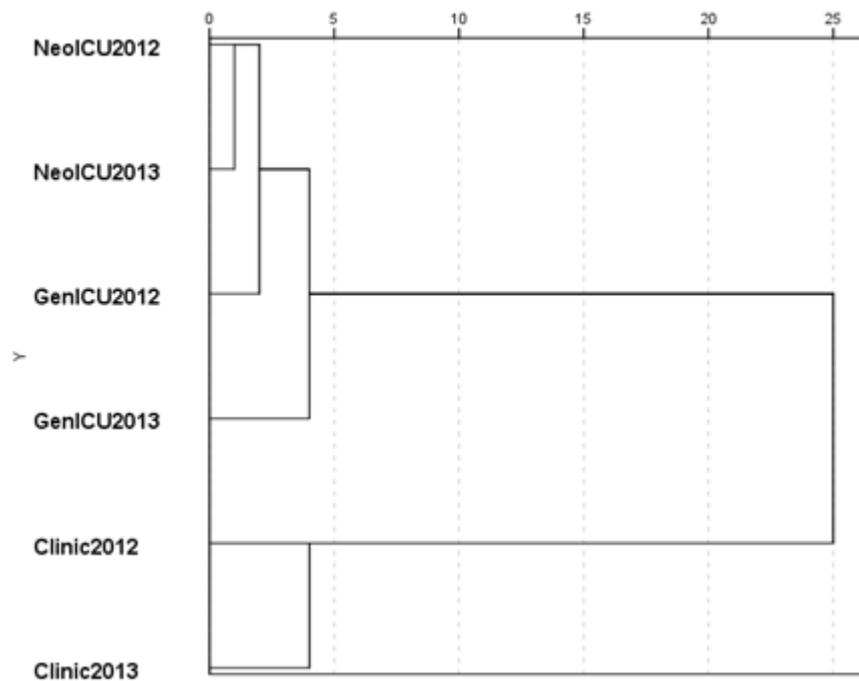
Table 1. Trends of prevalence rates among the different sectors of the University Hospital, 2012-2013.

Microorganisms	Sector of the HU-FURG											
	Medical Clinical				General – ICU				Neonatal – ICU			
	2012		2013		2012		2013		2012		2013	
	N	%	N	%	N	%	N	%	N	%	N	%
<i>Acinetobacter</i>												
<i>baumannii</i>	10	4.7	12	4.8	13	18.6	19	16.8	1	2.6	1	4.5
<i>Escherichia coli</i>	61	28.9	51	20.3	5	7.1	11	9.7	2	5.3	0	0.0
<i>Klebsiella</i>												
<i>pneumoniae</i>	34	16.1	31	12.4	6	8.6	14	12.4	6	15.8	1	4.5
<i>Proteus mirabilis</i>	10	4.7	19	7.6	3	4.3	2	1.8	0	0.0	0	0.0
<i>Pseudomonas</i>												
<i>aeruginosa</i>	22	10.4	33	13.1	7	10	24	21.2	5	13.2	0	0.0
<i>Staphylococcus</i>												
spp.	74	35.1	105	41.8	36	51.4	43	38.1	24	63.2	20	90.9
Total	211	100	251	100	70	100	113	100	38	100	22	100

Abbreviations: HU-FURG, University Hospital Dr. Miguel Riet Correa Jr.; ICU, Intensive Care Unit. Source: author.

The profile of the bacteria isolated in the study period (both in 2012 and in 2013) was grouped in the same cluster according to the hospital site, demonstrating the specificity of the different sectors in relation to these microbiota (Figure 1). The dendrogram illustrating the cluster analysis, based on microorganisms profile. The analysis of cases of infection in the years 2012/2013 in the neonatal intensive care unit shows a profile very close to similarity. As well, we can observe in the cluster, an approximation in the profile of microorganisms of the neonatal - ICU use in 2012 with the general - ICU use in the same year. The proximity between the profile of isolated microorganisms in the ICUs (neonatal and general) and in the medical clinic exists, however less evident than between the ICUs.

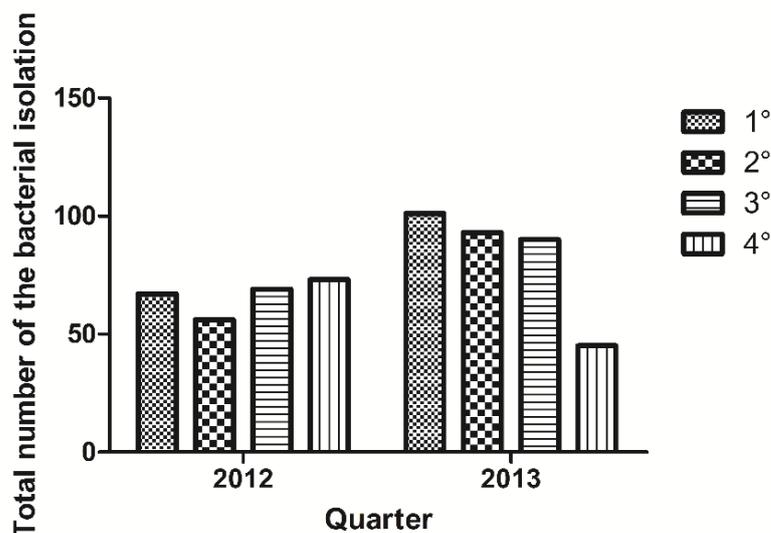
Figure 1. Dendrogram illustrating the results of the hierarchical cluster analysis of the profile of isolated microorganisms in each sector of the hospital in the years 2012 and 2013. Abbreviations: NeoICU2012 - Neonatal ICU isolates in 2012; NeoICU2013 - Neonatal ICU isolates in 2013; GenICU2012 - General ICU isolates in 2012; GenICU2013 - General ICU isolates in 2013; Clinic2012 - Clinic isolates in 2012; Clinic2013 - Clinic isolates in 2013.



Source: author.

There was a significant difference ($p < 0.05$) in the number of isolates in the three sectors in the four quarters of 2012 and 2013, using the chi-square test. In 2013, in general, there was an increase in the number of isolates of the species selected for analysis in this study compared to the year 2012, and from the second quarter of 2013 there was a reduction that culminated in approximately 50% in the last quarter of 2013 compared to the first quarter of the same year (Figure 2).

Figure 2. Total identification of bacterial infection at the University Hospital Dr. Miguel Riet Correa Jr. (HU-FURG) in four quarters of the years 2012 and 2013 ($p = 0.0003$).



Source: author.

The total antimicrobial consumption in the HU-FURG, either prophylactically or therapeutically, during the evaluation period was 3.865 units/dose, being 1,995 in the year 2012 and 1,870 units in the year 2013.

The most used groups were cephalosporins (21.5%), followed by the group of other β -lactams (penicillin and monobacchaemic group) (18.5%) and quinolones (12.6%). Antibiotics with decreased annual use were carbapenemics (1.4-fold), other β -lactams (1.4-fold) and sulphonamides (1.2-fold), in 2013 compared with 2012. According to the sector, in table 2 we can observe a greater use of aminoglycosides, cephalosporins and others β -lactams in neonatal - ICU, while in the medical clinic, besides cephalosporins and others β -lactams, the use of quinolones is also prominent. In general - ICU, a uniform pattern can be observed in the use of different classes of antibiotics.

A. baumannii, *K. pneumoniae* and *P. aeruginosa* were the microorganisms that had the highest number of isolates resistant to most of the antimicrobial classes evaluated. It should be noted that some data on the resistance profile were not found on some bacterial species, so possibly the tests were not performed or were not available during collection through the Phoenix system by the HU-FURG clinical analysis laboratory. In this context, we can highlight the lack of information on *S. aureus* species, in the three sectors and in the total period evaluated.

Table 2. Annual consumption of several representative classes of the antimicrobial agents at Dr. Miguel Riet Corrêa Jr. University Hospital (HU-FURG), 2012-2013. Abbreviations: HU-FURG - University Hospital Dr. Miguel Riet Correa Jr.; ICU – intensive Care Unit; Prophyl – prophylactic use; Therap – therapeutic use; AMG – aminoglycosides; CRB – carbapenems; CPH – cephalosporins; GLY – glycopeptide; LCM – lincosamides; MCR – macrolides; MTR – metronidolel; β -lac – β -lactams; QUI – quinolones; SUF – sulphonamides; TET – tetracycline.

Antibiotics	Sector of the HU-FURG/Year											
	Neonatal ICU Use (Unit)				Medical Clinical Use (Unit)				General ICU Use (Unit)			
	2012		2013		2012		2013		2012		2013	
	Prophyl	Therap	Prophyl	Therap	Prophyl	Therap	Prophyl	Therap	Prophyl	Therap	Prophyl	Therap
AMG	30	110	30	144	0	35	2	44	0	9	0	18
CRB	0	9	0	12	0	86	0	53	0	41	0	30
CPH	29	112	41	124	10	221	7	176	3	42	1	64
GLY	0	27	0	39	0	43	0	50	0	31	0	26
LCM	0	11	0	3	3	80	4	77	0	15	0	29
MCR	0	32	4	26	22	93	22	87	4	22	2	28
MTR	9	25	5	37	6	39	3	42	7	19	1	22
Others β -lac	31	169	31	148	6	185	0	94	1	28	0	22
QUI	0	3	0	2	18	209	15	193	3	15	1	27
SUF	5	2	1	5	34	45	24	33	3	12	5	14
TET	0	0	0	0	0	1	0	2	0	0	0	0
Total:	104	500	112	540	99	1037	77	851	21	234	10	280

Source: author.

A significant difference between the resistance antibiotics was observed in *A. baumannii*, *Proteus mirabilis* and *P. aeruginosa*. The increase in resistance rate with time ($p < 0.05$) was found for sulphonamides and tetracycline –resistant *A. baumannii* and the decrease in resistance rate ($p < 0.05$) for carbapenemics, sulphonamides and tetracycline-resistant *P. mirabilis* and carbapenems, sulphonamides and tetracycline-resistant *P. aeruginosa* (Table 3). In addition to these, we note the resistance of most of the *Staphylococcus haemolyticus* isolates to aminoglycosides, β -lactams and sulphonamides in both years of analysis.

Relationships between rates of main resistant pathogens isolated (*A. baumannii*, *P. mirabilis* and *P. aeruginosa*) and the annual consumption of the corresponding antibiotic (carbapenems, caphalosporins, sulfonamides and other β -lactams) in the hospital did not show significant positive associations (increased resistance associated with increased consumption). Significant negative associations (reduced resistance associated with reduced consumption) were found in the general ICU for cephalosporin -resistant *A. baumannii*, *P. mirabilis* and *P.*

aeruginosa.

Table 3. Trends of resistance rates among pathogens most prevalent in Dr. Miguel Riet Corrêa Jr. University Hospital (HU-FURG) infections, 2012-2013. Legends: *A.b.*: *Acinetobacter baumannii*; *E.c.*: *Escherichia coli*; *K.p.*: *Klebsiella pneumoniae*; *P.m.*: *Proteus mirabilis*; *P.a.*: *Pseudomonas aeruginosa*; *S.h.*: *Staphylococcus haemolyticus*; AMG – aminoglycosides; CRB – carbapenems; CPH – cephalosporins; Others β -lac – β -lactams; QUI – quinolones; SUF – sulphonamides; TET – tetracycline.

Antibiotics	Antimicrobial resistance (%)/Microorganism per year (N)											
	<i>A. b.*</i>		<i>E. c.</i>		<i>K.p.</i>		<i>P. m.*</i>		<i>P. a.*</i>		<i>S. h.</i>	
	2012 (24)	2013 (32)	2012 (68)	2013 (62)	2012 (46)	2013 (46)	2012 (13)	2013 (21)	2012 (34)	2013 (57)	2012 (29)	2013 (50)
AMG	73.3	80.0	32.5	30.0	43.3	42.5	33.3	35.0	36.6	26.6	80.0	80.0
CRB	100.0	73.3	0.0	0.0	0.0	5.0	100.0	55.0	55	32.5	-	-
CPH	82.0	88.0	48.3	60.0	71.0	58.0	26.0	33.7	80	80.8	-	-
Others β -lac	100.0	95.6	65.0	70.0	69.0	75.0	53.0	60.0	79	86.0	100.0	100.0
QUI	90.0	80.0	55.0	60.0	55.0	52.5	35.0	37.5	65	72.5	30.0	30.0
SUF	70.0	100.0	65.0	70.0	55.0	60.0	70.0	-	100	-	60.0	80.0
TET	20.0	50.0	56.0	80.0	65.0	80.0	100.0	60.0	100	-	35.0	20.0

* Statistically significant association ($p < 0.05$).

Source: author.

4. Discussion

This study regarding the association between antimicrobial resistance and antibiotic use at a HU-FURG discloses three important points. First, the notable trends in antimicrobial usage demonstrated an increase in the use of aminoglycosides in both prophylactic and therapeutic applications; second, the general use, mainly of the carbapenemics and other β -lactams in the hospital have been associated with the increase in or maintenance of the profile “resistant” in the isolates identified in the period of study; third, even with the reduction in the use of some classes, such as the class of “other β -lactams”. There was no significant reduction of resistant bacterial load, which may have been influenced by the short period of this study.

Among the studies that have been developed, gram-negative bacilli and species of the genus *Staphylococcus* spp. are the microorganisms predominantly identified as the cause of

this type of infection in the Brazilian medical institutes, corroborating the findings of this study (Oliveira, Kovner, & da Silva, 2010; Marra, et al., 2011). The total number of infections found in ICUs of this study, together, represented 33.57% of the total isolates in this study, surpassing the expected index for these sectors (approximately 20% of total infections in a hospital). These findings become even more important considering that an ICU patient is exposed to the risk of infection five to ten times greater, given his clinical condition and the variety of invasive procedures to which he is frequently submitted (Dasgupta, Chawan, & Hazra, 2015).

The antimicrobial administration should follow requirements beyond the type of prescription, therapeutic drug monitoring and the individualized dosing (Roberts, Joynt, & Choi, 2012). The prophylactic use of antimicrobials in our study occurred mainly in the neonatal ICU, whereas the therapeutic one was higher in the general ICU where invasive procedures occur in which complications can be predicted. In addition, in order to preserve the action of the antimicrobials available in the clinic, regardless of the type of prescription, whether through the use for prophylaxis, empirical or directed therapy, it should be reserved for situations where there is evidence that supports the use and / or the consequences of serious infections (Shah, et al., 2014).

Van Boeckel et al. (2014) evaluated the use of antimicrobials in the period 2000 to 2010, and identified the broad spectrum penicillins were the most used, followed by cephalosporins, macrolides and fluoroquinolones. This pattern was similar to that found in HU-FURG during the study period, where the most commonly used antimicrobials, regardless of the type of treatment, were cephalosporins, β -lactams and quinolones. The correlation between antimicrobial prescription and bacterial resistance index in our study revealed a nonuniform relationship for each bacterium, each antimicrobial agent and in each sector. Nevertheless, evaluating the increase of resistant isolates of *P. aeruginosa* to quinolones, we could verify that there was also an increase in the consumption of this class in the general ICU, and the resistance indexes of *P. mirabilis* seem to be associated with an increase in the consumption of aminoglycosides and cephalosporins in this sector of HU-FURG. In a study by Lee et al. (2010) the increase in the use of levofloxacin and ciprofloxacin, even with the low impact observed in the latter's resistance specifically, was positively correlated with the increase in resistance of *P. aeruginosa* to fluoroquinolones and their susceptibility was reestablished by the reduction in the use of levofloxacin (Lee, et al., 2010).

We can point out as main strategies to combat increasing bacterial resistance to the implementation of surveillance measures in order to optimize the use of antimicrobials, to

prevent the transmission and propagation of resistant microorganisms and to raise public awareness regarding the appropriate use of antimicrobials and development of new drugs effective in the treatment of these infections (Paphitou, 2013).

In conclusion, the correlation between antimicrobial prescription and bacterial resistance indices revealed a no uniform relationship for each bacterium, so we cannot associate only the indiscriminate use of antimicrobials with the increase of resistance, since it may be associated with other factors such as the awareness of health professionals, better surveillance measures and optimization of antimicrobial use.

5. Final Considerations

Furthermore, this study reveals the need for the dissemination and feedback of these data to clinicians and decision-makers at the hospital, as it may be crucial to improve policies for prescribing antibiotics and to implement effective infection control. In addition, future studies that promote the education in prescription and rational use of these drugs and assess the impacts of this process may contribute to reduce the morbidity and mortality of patients, the hospitalization periods and, consequently the expenses for the health service.

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