v. 2, n. 60, 2022

International Journal of Health Science

EVALUATION OF ANTIMICROBIAL CONSUMPTION IN UNITS OF ADULT INTENSIVE CARE: CORRELATION WITH BACTERIAL RESISTANCE

Alisson Soares Santos
ORCID: 0000-0002-0948-2822

Anderson Silva de Oliveira
ORCID: 0000-0003-2844-444X

Abstract: Inappropriate use of antimicrobials can lead to health, economic and social problems in both the short and long term. This is a cross-sectional study, carried out in the adult Intensive Care Units (ICU) of a General Hospital (HG) located in the Salvador Railway Suburb, Bahia, with the objective of evaluating the consumption of antimicrobials correlating with the incidence density of resistant bacteria. from 2014 to 2018. Antimicrobial consumption was obtained through the pharmacy's hospital management system, being evaluated and expressed through the defined daily dose (DDD) per 1000 patient-days. Data for the realization of incidence densities (ID) of resistant bacteria were obtained through the Hospital Infection Control Service (SCIH) system and expressed per 1000 patient-days. In evaluating the results, *Acinetobacter baumannii* resistant to carbapenems was the most isolated pathogen (6,87 DI_{1000}), the most consumed antimicrobial was piperacillin/tazobactam (231 DDD 1000) and among the correlations,*Klebsiella pneumoniae ceftriaxone resistant* and its consumption denoted to be one of the most important (R=0,396 e P=0,002). The study showed a decrease in the consumption of cefepime and teicoplanin and a high consumption of piperacillin/tazobactam and ceftriaxone, as well as a high incidence of some resistant bacteria, emphasizing the need and importance of better control of antimicrobial consumption, and dissemination of resistant strains.
Keywords: Consumption of antimicrobials. set daily dose. Bacterial resistance.

INTRODUCTION

The demonstrations carried out in the 19th century on the origins of infectious diseases encouraged researchers to seek specific substances to combat pathogenic microorganisms, with Paul Ehrlich being one of the first to create theories about the action of antimicrobials, and thanks to his work, researchers were able to obtain new products such as the discovery and synthesis of sulfamidic derivatives. Ehrlich and colleagues revolutionized therapeutics and the pharmaceutical industry, their studies having the main purpose of obtaining antimicrobial drugs of low toxicity for humans with the objective of being applied in systemic infections (PATRICK, 2012).

The in vitro discovery of the antibacterial action of sulfonamides in 1913 by Eisenberg initiated the research of Domagk, who in 1932 demonstrated the antibacterial activity of sulfa in vivo, raising the importance of these substances as medicinal drugs (TAVARES, 2014).

During and after the Second World War there were new findings and a great advance in the production of chemotherapeutics. The discovery of penicillin by Alexander Fleming ushered in a new era in medical practice bringing a solution to those suffering from infection.

As evidence of this action, in 1960 the first isolates of Staphylococcus aureus resistant to penicillin were found, and to overcome this problem methicillin was developed, which soon after its creation were found strains of Staphylococcus aureus resistant not only to methicillin, but to all beta-lactam antimicrobials already developed, these strains were called MRSA (Multiple Resistant Staphylococcus aureus) (LOWY, 1998).

According to ANVISA (2007, p.6), "the interpatient transmission of multidrug-resistant bacteria is more pronounced in ICUs, due to the lower adherence to hand hygiene associated with a high workload".

However, the consumption of antibacterials is a very important factor in the emergence of multidrug-resistant strains in ICUs, being related to the frequency, use of broad-

spectrum drugs, higher doses and longer duration of treatment, favoring the intensity and increasing the selective pressure on microorganisms (BERGNER et al., 2004; KERN et al., 2005).

Several organizations disclose strategies to monitor and manage antimicrobial consumption. Among the strategies used to obtain better results when it comes to the consumption of antimicrobials, the WHO indicates the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology to assist in the assessment of the consumption of antimicrobials used in health services.

The DDD is defined by the WHO Collaborating Center for Drug Statistics and Methodology as the average daily maintenance dose recommended for a specific drug used in adults, taking into consideration, its primary indication (WHO, 2018). The DDD is an international unit of measurement that allows you to trace a profile of drug use in the health establishment and compare consumption between hospitals in different regions, not necessarily reflecting the prescribed or recommended dose, thus, according to the W.H.O. – World Health Organization (2018), the DDD provides only a rough estimate of consumption, not expressing the actual usage exactly.

The research in question was born from the interest in knowing the profile of antimicrobial consumption in a hospital in the region of Salvador-BA, and to know how much the use of this class of drugs can influence the emergence of resistant strains.

GOALS

To evaluate the consumption of antimicrobials in the adult Intensive Care Units (ICU) of a General Hospital (HG) located in Salvador Railway Suburb `, Bahia, and to compare the consumption of antimicrobials from 2014 to 2018, correlating with the incidence density of resistant bacteria.

MATERIALS AND METHODS

HOSPITAL AND STUDY DESIGN

A cross-sectional and retrospective study was carried out in which data regarding the consumption of injectable antimicrobials, patient-day, resistance profile of bacterial isolates and site of pathogens collected between January 1, 2014 and December 31, 2018 were evaluated. carried out in the Adult Intensive Care Units (ICU) of a General Hospital (HG) located in Salvador Railway Suburb, Bahia, in which 50 ICU beds are available that serve the Unified Health System (SUS) through a Public-Private Partnership (PPP).

The research project was submitted to ``Plataforma Brasil`` and approved by the Research Ethics Committee of the Instituto Maintainer de Ensino Superior da Bahia - IMES with the Presentation Certificate for Ethical Appreciation (CAAE): 12217219.1.0000.5032, being also approved by the Research Center Gonçalo Moniz - FIOCRUZ/BA with CAAE: 12217219.1.3001.0040.

As this was a retrospective study, using secondary data (reports), the waiver of the Free and Informed Consent Term (FICT) was accepted.

ANTIMICROBIALS

The main systemic antibiotics defined in class J01 according to the Anatomical Therapeutic Chemical Classification or "Anatomical Therapeutic Chemical" (ATC) were used, excluding oral and topical antibiotics. Data on antimicrobial consumption was obtained through the pharmacy's hospital management system on a month-to-month basis during the study period. Antimicrobial consumption was converted to the Defined Daily Dose (DDD) per 1000 patient days according to the ATC/DDD Index 2019 of the World

Health Organization (WHO). The following antimicrobials were selected for evaluation: amikacin, ampicillin/sulbactam, cefepime, ceftriaxone, parenteral ciprofloxacin, clindamycin, imipenem, meropenem, oxacillin, piperacillin/tazobactam, polymyxin B, teicoplanin and vancomycin.

BACTERIAL RESISTANCE

For the study, the resistance profile of the main pathogenic bacteria isolated was analyzed, namely: Acinetobacter baumannii, Enterococcus sp, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae and Staphylococcus aureus. The data were obtained through the management system of the Hospital Infection Control Service (SCIH) and the data were collected on a monthly basis. During collection, the first isolate of each pathogen in each month per patient was considered, excluding duplicate isolates, that is, if the same pathogen was found in 2 or more different sites, in the same month, from the same patient, and with the same resistance profile, only one site would be chosen and the others discarded.

A priority order for site choice was used, with the following order: CSF, pleural fluid, peritoneal fluid, bronchoalveolar lavage, endotracheal aspirate, blood, urine, catheter tip and the other samples were classified as others. For the expression of the results and comparison with the consumption of antibacterial, the calculation of incidence density (ID) (number of isolates per 1000 patient-days) for resistant pathogens was used.

STATISTICAL ANALYSIS

For the correlation of antibacterial consumption and bacterial resistance, Spearman's nonparametric test was used. To assess the trend of antimicrobial consumption and the propensity of resistant pathogens, the Jonckheere-Terpstra test was used. All analyzes used monthly data, with a significance level and alpha error ≤ 5%. Statistical analyzes were performed using SPSS 25® (IBM, Corp) and Microsoft Excel 2019® (Microsoft, Corp).

RESULTS

ANTIMICROBIAL CONSUMPTION

During the 5 years of study, there were a total of 87,613 patients per day, with an average of 17,522 patients per day per year. The annual consumption of antimicrobials was evaluated on a monthly basis and expressed in DDD/1000 patient-days (Figure 1).

The year 2015 was the period with the highest antimicrobial consumption among the years evaluated, with an average of (107 DDD_{1000}), followed by 2016 (100,6 DDD_{1000}), 2018 (99,3 DDD_{1000}), 2014 (98,5 DDD_{1000}), e 2017 (94,5 DDD_{1000}). Between the years 2014 to 2015 there was an increase of 8%, from 2015 to 2016 a drop of 6%, from 2016 to 2017 a new drop of 6%, from 2017 to 2018 a 5% increase in consumption among the antimicrobials evaluated.

During the study period, the most consumed antimicrobials were pyreracillin in association with tazobactam (231 DDD_{1000}), followed by the oxacillin (226 DDD_{1000}), meropenem (204 DDD_{1000}), ceftriaxone (198,1 DDD_{1000}), teicoplanin with (152 DDD_{1000}), polymyxin B (111 DDD_{1000}), and clindamycin with (91,1 DDD_{1000}) (Figure 2).

TRENDS IN ANTIMICROBIAL CONSUMPTION

The annual assessment of antimicrobial consumption shows that over the 5-year study period, a reduction in the consumption of some antimicrobials was observed, among them, cefepime with (12,5 DDD_{1000} in 2014, getting at 3,3 DDD_{1000} in 2018, P=0,003), ciprofloxacin (23,4 DDD_{1000} ib 2014; 7,4 DDD_{1000} in 2018, P=<0,001), teicoplanin

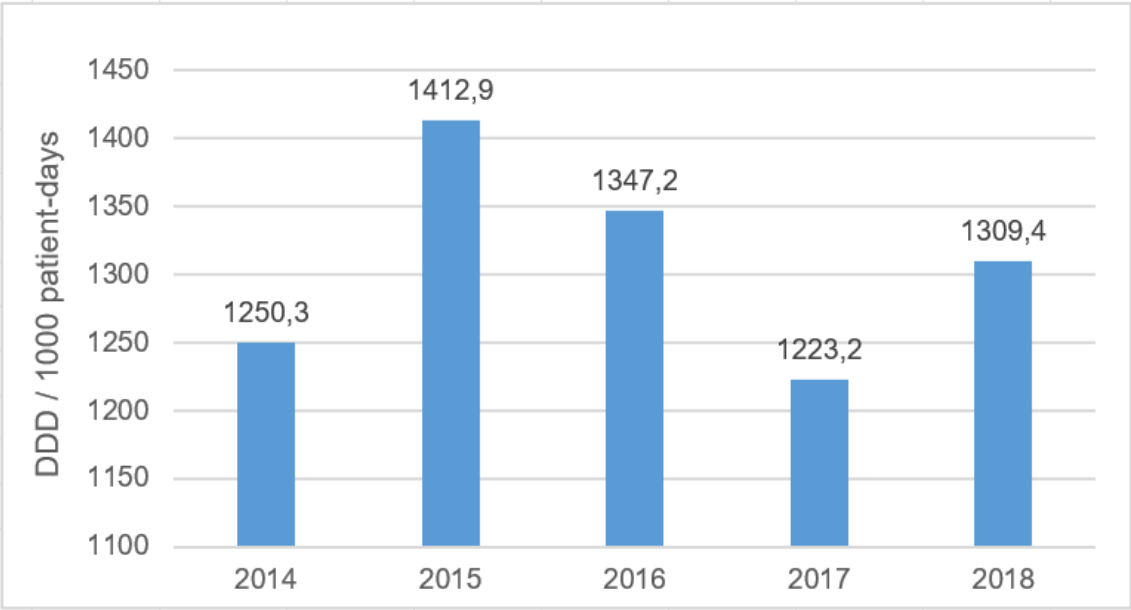


Figure 1 - Annual antimicrobial consumption, expressed in DDD/1000 patient-day

Source: Own authorship (2019)

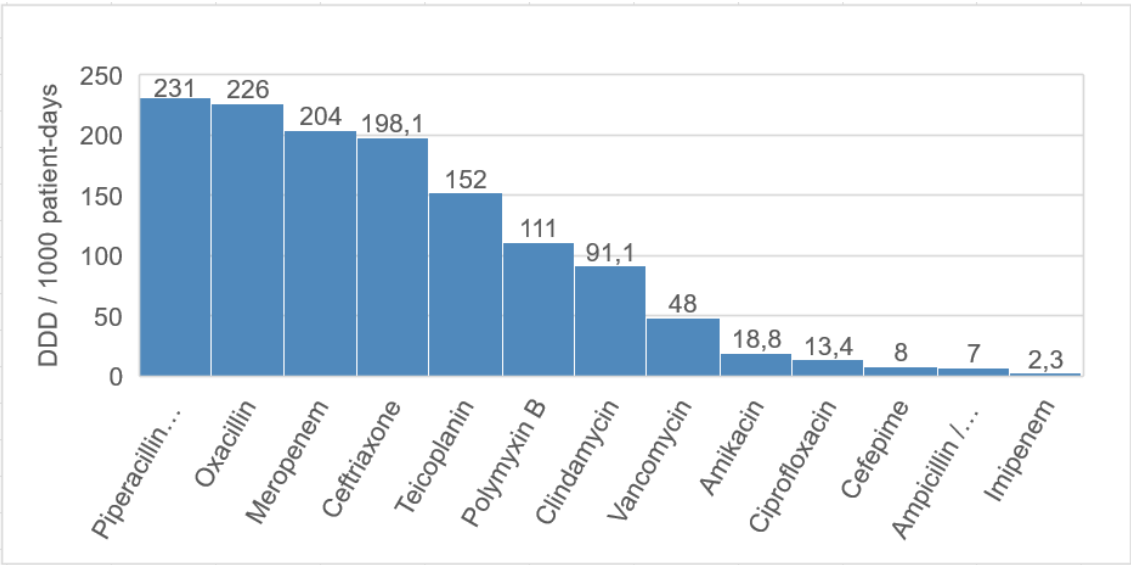


Figure 2 - Descending order of the main antimicrobials consumed during the study period in DDD/1000 patient-day

Source: Own authorship (2019)

(227,8 DDD_{1000} in 2014; 94,4 DDD_{1000} in 2018, *P*=<0,001) and meropenem (225,2 DDD_{1000} in 2014; 191 DDD_{1000} in 2018), despite no significant difference, (*P*=0,083) (Table 1).

Despite the reductions, an increase in ceftriaxone consumption was also noted (132,8 DDD_{1000} em 2014, achieving 246,3 DDD_{1000} in 2018, *P*=<0,001), clindamycin (15,9 DDD_{1000} em 2014; 129,7 DDD_{1000} em 2018, *P*=<0,001) and ampicillin in combination with tazobactam 3,1 DDD_{1000} in 2014; 9,3 DDD_{1000} in 2018, P=0.002).

The most consumed antimicrobial in 2014 was piperacillin in association with tazobactam (256,4 DDD_{1000}), in 2015 and 2016 oxacillin with (326,9 DDD_{1000}) and (291 DDD_{1000}) respectively, 2017 ceftriaxone(231,4 DDD_{1000}) and 2018 again ceftriaxone with (246 DDD_{1000}).

BACTERIAL RESISTANCE

During the study period, 987 resistant bacteria were observed, with 318 strains of *Acinetobacter baumannii* (32%), 153 strains of *Pseudomonas aeruginosa* (16%), 304 of *Klebsiella pneumoniae* (31%), 118 of *Escherichia coli* (12%), 86 *Staphylococcus aureus* (9%) and 8 strains of *Enterococcus sp* (1%), the latter was ruled out due to the low incidence density presented, despite its high epidemiological importance (Figure 3).

Among the selected sites, the endotracheal aspirate was the main sample where resistant pathogens were isolated (35.5%), followed by blood (29.7%), peritoneal fluid (7.4%), catheter tip (7.3%). %), urine (7.0%), bronchoalveolar lavage with (3.6%), pleural fluid (0.8%), cerebrospinal fluid (0.3%), and others accounted for (8.4%) of the samples.

BACTERIAL RESISTANCE TREND

There was a significant decrease in the incidence density of *Acinetobacter baumannii* resistant to cefepime (3.66 in 2014; 2.57 in 2018, P=0.018) and to carbapenems (8.0 in 2014; 4.80 in 2018, P=0.002). Regarding the incidence density of ceftriaxone-resistant Escherichia coli, an increase was observed (0.74 in 2014; 1.77 in 2018, P=0.025). Resistant strains of *Pseudomonas aeruginosa* remained stable throughout the study period, with a significant increase from 2017 to 2018.

A substantial increase in the incidence density of ampicillin-resistant *Klebsiella pneumoniae* was observed in association with sulbactam (1.66 in 2014 and 5.14 in 2018, P=<0.001), ceftriaxone (1.83 in 2014 and 5.82 in 2018, P=<0.001), carbapenems (0.46 in 2014; 3.71 in 2018, P=<0.001), piperacillin in association with tazobactam (1.20 in 2014 and 4.11 in 2018, P=< 0.001) and increase in extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* (1.54 in 2014 and 3.77 in 2018, P=0.001) (Figure 4).

There were no significant changes in relation to *Staphylococcus aureus* resistent to oxacillin (Table 2). Between 2014 and 2017, the most isolated resistant pathogen was *Acinetobacter baumannii* resistant to carbapenems (8.0 in 2014; 9.18 in 2015; 6.96 in 2016 and 5.39 in 2017), *Klebsiella pneumoniae* resistant to ceftriaxone was the most isolated in 2018 (5.82).

CORRELATION BETWEEN ANTIBACTERIAL CONSUMPTION AND BACTERIAL RESISTANCE

The correlations between bacterial resistance and antimicrobial consumption are described in Table 3. Despite the trend of consumption of ciprofloxacin and carbapenems being similar in comparison with the incidence density of *Pseudomonas aeruginosa*, only the consumption of piperacillin in association with tazobactam showed a positive correlation significant (R=0.393 and P=0.002), showing a similar trend (Figure 5). Cefepime consumption and

Code ATC	Antimicrobial	DDD per 1000 patients day						
		2014	2015	2016	2017	2018	p-valor*	2014-2018
J01GB06	Amikacin	7,2	35,6	13,6	22,6	15,1	0,062	18,8
J01CR01	Ampicillin/sulbactam	3,1	1,2	12,2	9,2	9,3	0,002	7,0
J01DE01	Cefepime	12,5	10,0	9,0	5,3	3,3	0,003	8,0
J01DD04	Ceftriaxone	132,8	168,9	211,5	231,4	246,3	<0,001	198,1
J01MA02	ciprofloxacin parenteral	23,4	17,7	8,4	10,0	7,4	<0,001	13,4
J01FF01	Clindamycin	15,9	77,4	117,8	115	129,7	<0,001	91,1
J01DH51	Imipenem	1,0	1,9	2,9	5,5	0,0	0,220	2,3
J01DH02	Meropenem	225,2	216,0	184,6	202,8	191,0	0,083	204,0
J01CF04	Oxacillin	202,8	326,9	291,0	64,2	241,4	0,361	226,0
J01CR05	Piperacillin/tazobactam	256,4	225,4	211,3	224,2	235,7	0,328	231,0
J01XB02	polymyxin B	97,2	118,8	116,2	142,2	79,3	0,715	111,0
J01XA02	Teicoplanin	227,8	168,2	119,6	147,9	94,4	<0,001	152,0
J01XA01	Vancomycin	45,0	44,9	49,1	42,9	56,5	0,192	48,0

Table 1 - Defined Daily Dose (DDD) of the main antimicrobials consumed during the period.

* Jonckheere-Terpstra test.

Source: Own authorship (2019).

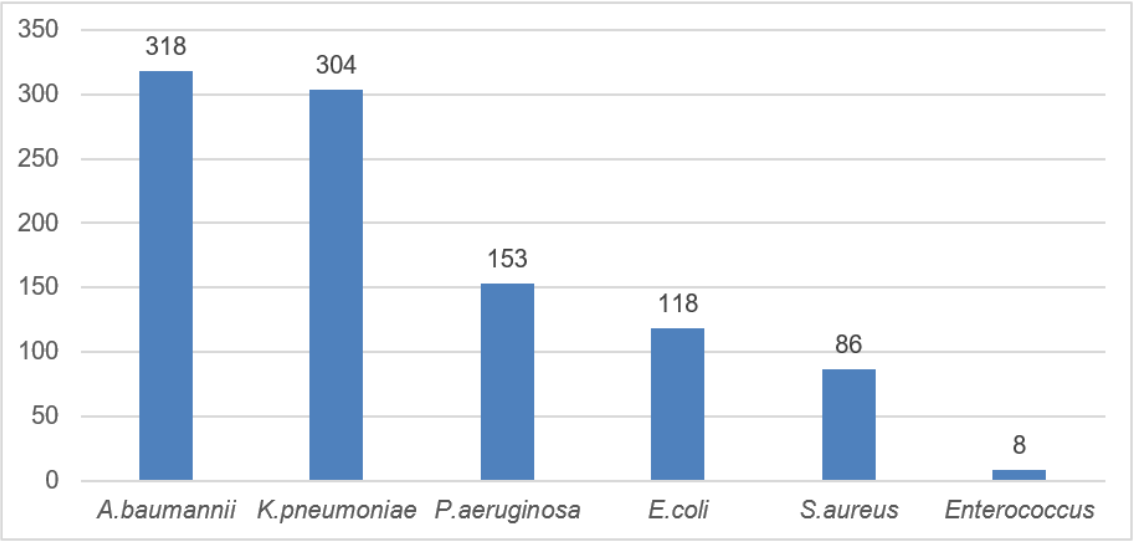


Figure 3 - Proportion of resistant strains isolated

Source: Own authorship (2019).

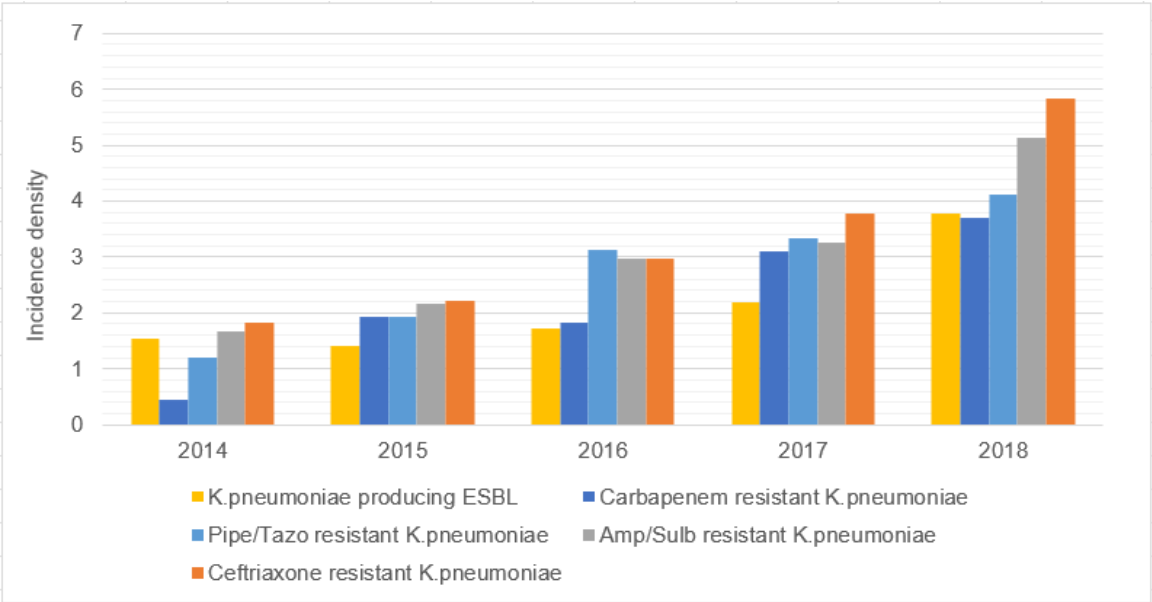


Figure 4 – K.*pneumoniae* resistance from 2014 to 2018.

Pipe/tazo = Piperacillin in association with tazobactam

Amp/Sulb = Ampicillin in association with sulbactam

Source: Own authorship (2019).

Bacterium	Antimicrobial	DI per 1000 patients day						
		2014	2015	2016	2017	2018	p-valor*	2014-2018
Acinetobacter baumannii	Amikacin	1,66	1,53	0,74	1,20	0,74	0,064	1,18
	Cefepime	3,66	4,76	3,65	2,81	2,57	0,018	3,49
	Carbapenems	8,00	9,18	6,96	5,39	4,80	0,002	6,87
Escherichia coli	Amikacin	0,11	0,00	0,06	0,06	0,06	0,733	0,07
	Amp/Sulb	1,03	0,91	1,08	0,80	1,66	0,399	1,10
	Ceftriaxone	0,74	0,85	0,68	0,86	1,77	0,025	0,98
	Ciprofloxacin	1,03	0,91	0,91	0,63	1,14	0,910	0,92
	ESBL	0,63	0,74	0,40	0,86	1,66	0,023	0,86
	carbapenems	0,11	0,17	0,11	0,00	0,23	0,950	0,13
	Pipe/Tazo	0,63	0,51	0,74	0,40	0,63	0,143	0,58
Pseudomonas aeruginosa	Amikacin	0,51	0,62	0,63	0,11	0,51	0,205	0,48
	Cefepime	1,14	1,19	1,03	0,52	1,60	0,782	1,10
	Ceftazidime	1,31	1,19	1,08	0,63	1,77	0,974	1,20
	Ciprofloxacin	0,74	0,85	0,68	0,11	0,63	0,161	0,60
	Carbapenems	3,54	2,27	2,05	2,18	2,40	0,185	2,49
	Pipe/Tazo	1,20	0,96	0,97	0,57	1,43	0,895	1,03
Klebsiella pneumoniae	Amp + Sulb	1,66	2,15	2,97	3,27	5,14	<0,001	3,04
	ceftriaxone	1,83	2,21	2,97	3,79	5,82	<0,001	3,32
	ESBL	1,54	1,42	1,71	2,18	3,77	0,001	2,12
	carbapenems	0,46	1,93	1,83	3,10	3,71	<0,001	2,20
	Pipe/Tazo	1,20	1,93	3,14	3,33	4,11	<0,001	2,74

Staphylococcus aureus	Oxacillin	1,09	0,34	0,51	0,63	0,40	0,211	0,59

* Jonckheere-Terpstra test;

Amp/Sulb = Ampicillin in association with sulbactam;

Carbapenems = meropenem + imipenem;

Pipe/Tazo = Piperacilina em associação com tazobactam;

ESBL = Extended Spectrum Beta-lactamase

Table 2 - Incidence density of resistant isolates

Source: Own authorship (2019).

Bacterium	Bacterial resistance		Antibiotic consumption		Correlation	
	Resistance	Tendency	Antibiotic	Tendency	p-value*	Coef. of correlation
Acinetobacter baumannii	Amikacin	↓	amikacin	↑	0,513	0,086
	Cefepime	↓	Cefepime	↓	0,081	0,227
	carbapenems	↓	carbapenems	↓	0,079	0,229
Escherichia coli	amikacin	↓	amikacin	↑	0,212	-0,164
	Amp/Sulb	↑	Amp/Sulb	↑	0,494	0,090
	ceftriaxone	↑	Cceftriaxone	↑	0,152	0,187
	ciprofloxacin	↔	ciprofloxacin	↓	0,875	0,021
	ESBL	↑	β-lactams	↑	0,235	0,156
	carbapenems	↑	carbapenems	↓	0,819	0,030
	Pipe/Tazo	↔	Pipe/Tazo	↔	0,335	-0,127
Pseudomonas aeruginosa	amikacin	↓	amikacin	↑	0,630	0,063
	Cefepime	↑	Cefepime	↓	0,741	-0,043
	ciprofloxacin	↓	ciprofloxacin	↓	0,218	0,161
	carbapenems	↓	carbapenems	↓	0,230	0,157
			ceftriaxone	↑	0,016	-0,310
	Pipe/Tazo	↔	Pipe/Tazo	↔	0,002	0,393
Klebsiella pneumoniae	Amp + Sulb	↑	Amp + Sulb	↑	0,234	0,156
	ceftriaxone	↑	ceftriaxone	↑	0,002	0,396
	ESBL	↑	β-lactâmicos	↑	0,054	0,250
	Carbapenêmicos	↑	Carbapenêmicos	↓	0,184	-0,174
			Ceftriaxona	↑	0,003	0,373
	Pipe/Tazo	↑	Pipe/Tazo	↔	0,716	-0,048
Staphylococcus aureus	Oxacilina	↓	Oxacilina	↓	0,383	-0,115

Amp/Sulb = Ampicillin in association with sulbactam; Carbapenems = meropenem and imipenem;

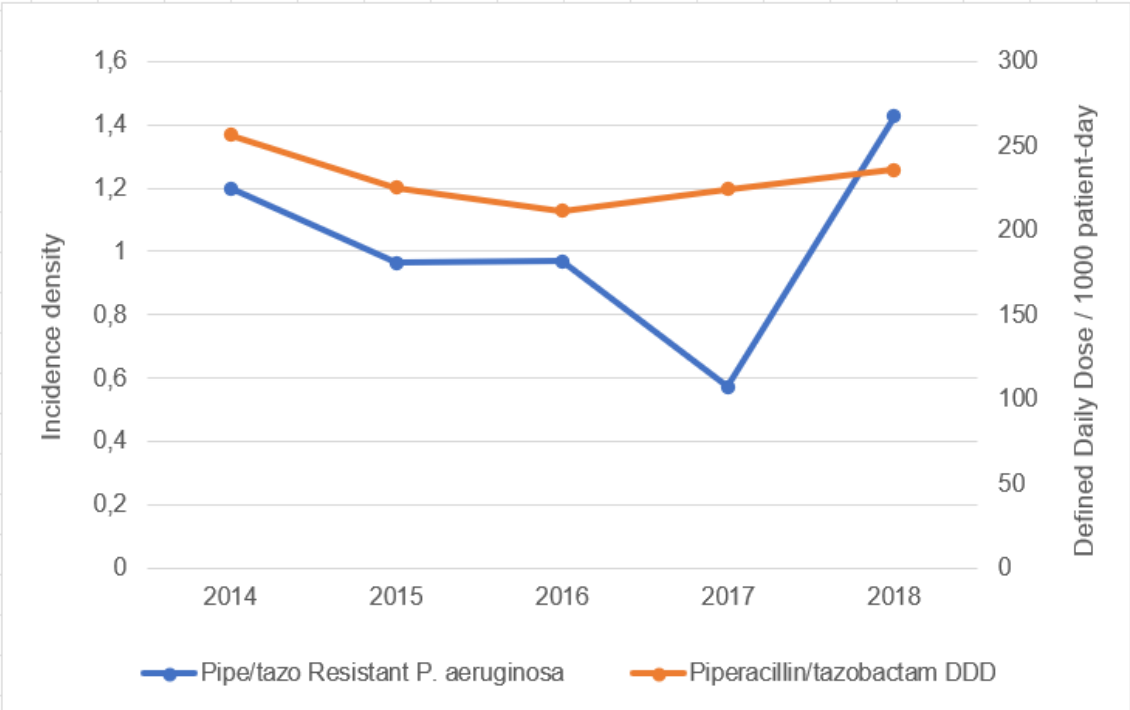
Pipe/Tazo = Piperacillin in association with tazobactam; ESBL = Spectrum Beta-lactamase; extended. β-lactams = carbapenems, cephalosporins, ampicillin/sulbactam; piperacillin/tazobactam. Coef. of correlation = Correlation coefficient;

↑ = Increasing trend; ↔ = Constant trend; ↓ = Decreasing trend;

* Spearman on a month basis;

Table 3 - Correlation between antibacterial consumption (DDD) and incidence density of resistant bacteria (DI)

Source: Own authorship (2019).



Pipe/tazo = Piperacillin in association with tazobactam

Figure 5 - **Pseudomonas aeruginosa** incidence density x DDD Pipe/tazo

Source: Own authorship (2019).

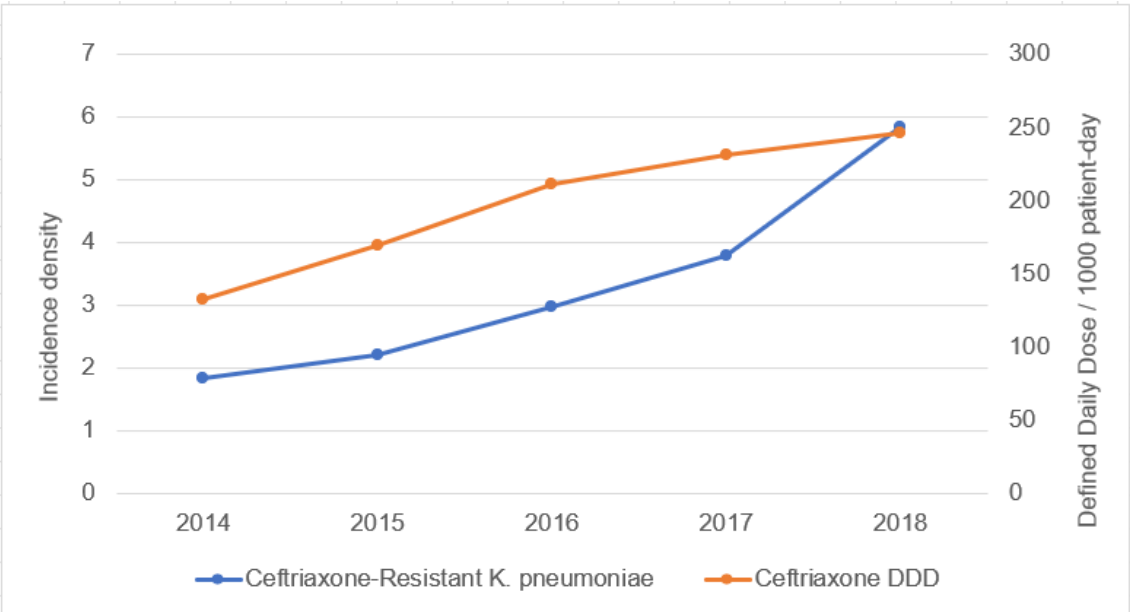


Figure 6 - Incidence density of Klebsiella pneumoniae x DDD ceftriaxone

Source: Own authorship (2019).

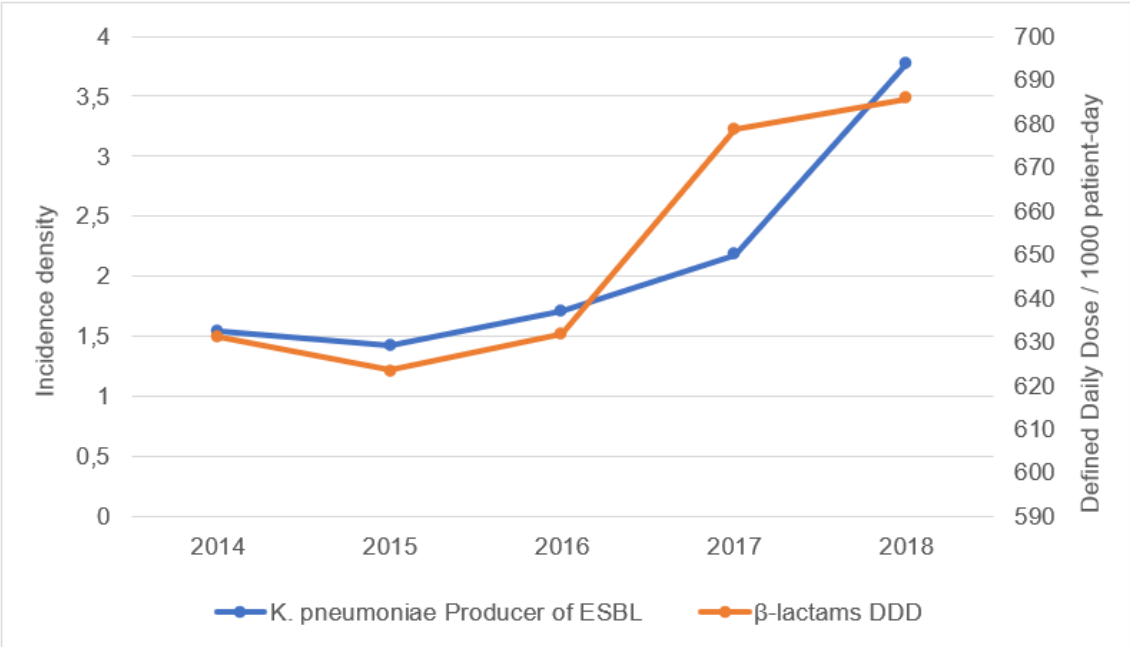


Figure 7 - Incidence density of *Klebsiella pneumoniae* Extended Spectrum Beta-lactamase producer x DDD Beta-lactams

Source: Own authorship (2019).

resistant Pseudomonas aeruginosa isolates showed opposite trends.

There was a positive correlation between ceftriaxone-resistant Klebsiella pneumoniae and antibiotic consumption (R=0.396 and P=0.002), (Figure 6) and a correlation between carbapenem-resistant Klebsiella pneumoniae and ceftriaxone consumption (R=0.373 and P= 0.003). A correlation was also observed between extended-spectrum beta-lactamase-producing Klebsiella pneumoniae and beta-lactams (R=0.396 and P=0.054), demonstrating an increase in consumption in both correlations (Figure 7).

The same happened with *Acinetobacter baumannii* resistant to cefepime and carbapenems, which despite showing a downward trend regarding the incidence density and consumption of such antibacterials, did not show statistically significant results. The resistance of *Staphylococcus aureus* oxacillin showed no significant correlation when compared to antibiotic consumption despite showing similar downward trends.

DISCUSSION

ANTIBACTERIAL CONSUMPTION

The emergence of resistant bacteria has received increasing attention in recent years due to the compromise of therapeutic efficacy in the control of bacterial infections. According to the WHO (2005), the emergence of resistant bacteria is the cause of a natural phenomenon when using antimicrobials, but this rise is being accelerated by the inappropriate use of this class of drugs.

The analyzes of the present study showed that during the evaluated period, the most consumed antibiotic was piperacillin/tazobactam, which has a constant consumption over the years, but high compared to the literature that demonstrates cephalosporins as the most consumed class according to the study. by Kim (2018) and Tsutsui (2018), but the study by Balkhy (2018) reports that carbapenems were the most consumed class in a period of 33 months evaluated in a hospital in Saudi Arabia.

Oxacillin unexpectedly occupies second place in which it is not expressive in scientific works that try to evaluate consumption, perhaps because of the resistance of Staphylococcus aureus to oxacillin occurs by mutation, leading to the lack of interest of studies in approaching it, however, such consumption can be explained by a high rate of gram-positive coagulase negative isolates.

Polymyxin B, considered one of the drugs of last choice for the treatment of resistant bacteria, also presented an unexpected consumption, ahead of clindamycin, which has a high consumption trend, ciprofloxacin and cefepime, which has been less and less used.

Meropenem was the third most consumed antibacterial during the study period, with a DDD of 204.3 per 1000 patient-days, a result that would be different if the WHO did not present a new standard DDD for the antibiotic in November 2018, changing its value from 2 to 3, if the analyzes used the previous value, meropenem would express a DDD of 305.8 per 1000 patient-days, becoming the largest antimicrobial consumed during the study period with a 32% margin of difference for the second place, being the comparison with other works harmed due to changes in the ATC/DDD carried out over the years, in addition to the studies grouping antimicrobials differently from each other and most studies using the DDD, using the indicator of 100 bed-days.

In fourth place is ceftriaxone with high, increasing and significant consumption values, becoming the most consumed antimicrobial in the last two years.

BACTERIAL RESISTANCE

During the study period, most isolates

were obtained from endotracheal aspirate (35%) and blood (30%). In most of the selected studies, the pathogen collection sites were not found, but the study by Carneiro (2006), carried out in a regional hospital in Brasília, informs that 31.5% of the isolates were obtained from blood, demonstrating similarity between the obtained results.

Acinetobacter baumannii was the most isolated resistant pathogen among the selected bacteria (32%), predominating from 2014 to 2017, with an incidence density (ID) of 6.87 for carbapenem-resistant isolates, with a decrease in ID for strains resistant to carbapenems. cefepime (30%) and carbapenems (40%) from 2014 to 2018. Other studies did not show relevant changes in the emergence of such strains, such as the work by Barberi (2017) who showed an ID below 1, as well as the study by Carneiro (2006), reporting that 60% of Acinetobacter baumannii isolates were resistant to ceftazidime and amikacin, with only 0.1 of DI for strains resistant to carbapenems, a value much lower than in the present study.

From 2014 to 2018, there was a steady increase in the emergence of strains of Klebsiella pneumoniae resistant to carbapenems, ampicillin/sulbactam, piperacillin/tazobactam, producer of extended-spectrum beta-lactamase and ceftriaxone, the latter being the most isolated type of resistance in 2018 The marked emergence of resistant isolates of Klebsiella pneumoniae was also evidenced in other studies such as that of Barberi (2017), which despite showing a significant trend, only showed a statistical difference for strains resistant to piperacillin/tazobactam. On the other hand, Pseudomonas aeruginosa did not find significant changes in its ID, with resistance to carbapenems being the most common during the period. These divergences can be explained by the difference in the microbiological profile of each region.

CORRELATION BETWEEN ANTIBACTERIAL CONSUMPTION AND BACTERIAL RESISTANCE

A positive correlation was found between the high incidence density of *ceftriaxone-resistant Klebsiella pneumoniae* in relation to the consumption of the same antimicrobial (R=0.396 and P=0.002). A positive correlation was also found between extended-spectrum beta-lactamase-producing Klebsiella pneumoniae and beta-lactams (R=0.250 and P=0.054). As well as a correlation between carbapenem-resistant Klebsiella *pneumoniae* and *ceftriaxone* consumption (R=0.373 and P=0.003).

In the study by Kim (2018), antibiotics were grouped into classes and a correlation was observed between third-generation cephalosporin-resistant *Klebsiella pneumoniae* in relation to the consumption of fluoroquinolones, aminoglycosides, carbapenems and beta-lactams/beta-lactamase inhibitors, but not a significant correlation was found in relation to the group of third-generation cephalosporins in which *ceftriaxone* is included, however, in the study by Prakobsrikul (2019), a positive correlation was evidenced between carbapenem-resistant *Klebsiella pneumoniae* and the consumption of ceftriaxone, a result that is similar to that found in the present study.

It was not found in the selected works analysis of *Klebsiella pneumoniae* extended-spectrum beta-lactamase producer compared to antibiotics.

A significant positive correlation was noted between piperacillin/tazobactam-resistant *Pseudomonas aeruginosa* and antibacterial consumption (R=0.393 and P=0.002). Similarities were observed between the result obtained and the study by Carneiro (2006), in which he demonstrated a positive correlation between *Pseudomonas aeruginosa* resistant to piperacillin/tazobactam and the consumption

of the same antibiotic, the study also showed a positive correlation between Pseudomonas aeruginosa resistant to carbapenems and the its consumption, as well, showed a negative correlation when comparing *Pseudomonas aeruginosa* resistant to amikacin and the use of the same antimicrobial, results not seen in our study.

CONCLUSION

The consumption of antimicrobials in the adult ICUs of the Hospital from 2014 to 2018 showed, in part, similarity with the literature, when it expresses high consumption of cephalosporins, but it did not prove to be the most consumed, but piperacillin/tazobactam with constant growth over the years. years, also found in the literature, followed by oxacillin, both expressing values above those observed in scientific works.

The DDD, because it was updated on November 28, 2018, reduced the value of meropenem, which would be the most consumed during the study period if there was no such change, which weakens the comparability of this antibiotic with other works.

Regarding the incidence density of resistant bacteria, *Acinetobacter baumannii* resistant to carbapenems, despite being the most isolated during the study period, showed a significant decrease over the years, however *Klebsiella pneumoniae* has shown high values in relation to all resistances evaluated in the study, with resistance to ceftriaxone being the most significant increase. The literature shows the increase mentioned, however, not so accelerated and expressive compared to the values found.

The positive correlation between antibacterial consumption and bacterial resistance evidenced in the present study was, Pseudomonas aeruginosa resistant to piperacilina/tazobactam and consumption of antibacterial, *Klebsiella pneumoniae* resistant to ceftriaxone and the use of the same antimicrobial, being also evidenced the correlation between strains resistant to carbapenems and the consumption of ceftriaxone, such findings are confirmed with the scientific works, however, it was not found in the literature, comparison between *Klebsiella pneumoniae* Extended-spectrum beta-lactamase producer correlated with the use of antibiotics, however, in the present study, a positive correlation of such a strain was found in relation to the consumption of beta-lactams.

The methodologies used to identify the profile of antimicrobial consumption and the incidence density of resistant bacteria also highlight, through correlation, the need and importance of better control of antimicrobial consumption, and dissemination of resistant strains.

REFERENCES

ANVISA. Agência Nacional de Vigilância Sanitária. **Investigação e controle de bactérias multirresistentes**. Brasília-DF, 2007. Disponível em: <http://anvisa.gov.br/servicosaude/controle/reniss/manual%20_controle_bacterias.pdf >. Acesso em: 09 dez. 2018.

BALKHY, HANAN H. et al. Antimicrobial consumption in five adult intensive care units: a 33-month surveillance study. **Antimicrobial Resistance & Infection Control**, v. 7, n. 1, p. 156, 2018. Disponível em:< https://www.ncbi.nlm.nih.gov/pubmed/30598819>. Acesso em: 17 jun. 2019.

BARBERI G, DE COLA MC, DELL'UTRI C. et al. Antimicrobial consumption and antimicrobial resistance: a snapshot of an Italian neuromuscular rehabilitation center. **New Microbiol**, v. 40, p. 119-129, 2017. Disponível em:< https://www.ncbi.nlm.nih.gov/pubmed/28368076 >. Acesso em: 28 mai. 2019.

BERGNER J, BÜHNER R, DÖRJE F. et al. Antibiotic use in German university hospitals 1998–2000 (Project INTERUNI-II). **International journal of antimicrobial agents,** v. 24, n. 3, p. 213-218, 2004. ISSN 0924-8579. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15325423 >. Acesso em: 12 dez. 2018.

CARNEIRO, J. **Padrão de consumo de antibacterianos em uma UTI geral: correlação com a resistência bacteriana**. Brasilia, 2006. Disponível em: < https://core.ac.uk/download/pdf/33532174.pdf >.Acesso em: 04 nov. 2018.

KERN W, STEIB-BAUERT M, FELLHAUER M. et al. Antibiotic Use in Non–University Regional Acute Care General Hospitals in Southwestern Germany, 2001–2002. **Infection,** v. 33, n. 5-6, p. 333-339, 2005. ISSN 0300-8126.

KIM B, KIM Y, HWANG H. et al. Trends and correlation between antibiotic usage and resistance pattern among hospitalized patients at university hospitals in Korea, 2004 to 2012: A nationwide multicenter study. **Medicine**, v. 97, n. 51, 2018. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30572507 >. Acesso em: 28 mai. 2019.

LOWY, F. D. Staphylococcus aureus infections. **New England journal of medicine**, v. 339, n. 8, p. 520-532, 1998. ISSN 0028-4793. Disponível em: < https://www.nejm.org/doi/full/10.1056/nejm199808203390806 >. Acesso em: 14 nov. 2018.

NOSSA, C. Alexander Fleming e a descoberta da penicilina. **Jornal Brasileiro de Patologia e Medicina Laboratorial** v. 45, p. I, 2009. ISSN 1676-2444. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S167624442009000500001&nrm=iso >. Acesso em: 06 nov. 2018.

PATRICK, G. L. **An introduction to medicinal chemistry**. 5 ed. Oxford university press, New York, 2013. ISBN 0199697396.

PRAKOBSRIKUL N, MALATHUM K, SANTANIRAND P. et al. Correlation between antimicrobial consumption and the prevalence of carbapenem-resistant Escherichia coli and carbapenem-resistant Klebsiella pneumoniae at a university hospital in Thailand. **Journal of clinical pharmacy and therapeutics**, v. 44, n. 2, p. 292-299, 2019. Disponível em:< https://www.ncbi.nlm.nih.gov/pubmed/30578578 >. Acesso em: 28 mai. 2019.

TAVARES, W. Introdução ao estudo dos antimicrobianos. In: ATHENEU (Ed.). **Manual de antibióticos e Quimioterapicos antiinfecciosos**. 3 ed., São Paulo, 2014.

TSUTSUI, A; YAHARA, K; SHIBAYAMA, K. Trends and patterns of national antimicrobial consumption in Japan from 2004 to 2016. **Journal of infection and chemotherapy**, v. 24, n. 6, p. 414-421, 2018. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29428566 >. Acesso em: 28 mai. 2019.

WHO COLLABORATING CENTER FOR DRUG STATISTICS METHODOLOGY. **Implementation and maintenance of the ATC/DDD methodology**. WORLD HEALTH ORGANIZATION. 15 fev. 2018. Disponível em: < https://www.whocc.no/use_of_atc_ddd >. Acesso em: 13 out. 2018.

WORLD HEALTH ORGANIZATION. Containing antimicrobial resistance. **WHO Policy Perspectives on Medicines**, n. 10, Geneva, 2005. Disponível em: < http://www.who.int/management/anmicrobialresistance.pdf >. Acesso em: 14 nov. 2018.