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Major Article

Antimicrobial use, incidence, etiology and resistance patterns in bacteria causing ventilator-associated pneumonia in a clinical-surgical intensive care unit

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ABSTRACT

Introduction: Antimicrobial resistance is an increasing threat in hospitalized patients, and inappropriate empirical antimicrobial therapy is known to adversely affect outcomes in ventilator-associated pneumonia (VAP). The aim of this study was to evaluate antimicrobial usage, incidence, etiology, and antimicrobial resistance trends for prominent nosocomial pathogens causing ventilator-associated pneumonia in a clinical-surgical intensive care unit (ICU). **Methods**: Gram-negative bacilli and *Staphylococcus aureus* causing VAP, as well as their antimicrobial resistance patterns and data on consumption (defined daily dose [DDD] per 1,000 patient days) of glycopeptides, extended-spectrum cephalosporins, and carbapenems in the unit were evaluated in two different periods (A and B). **Results:** Antimicrobial use was high, mainly of broad-spectrum cephalosporins, with a significant increase in the consumption of glycopeptides ($p < 0.0001$) and carbapenems ($p < 0.007$) in period B. For *Acinetobacter baumannii* and members of the Enterobacteriaceae family, 5.27- and 3.06-fold increases in VAPs, respectively, were noted, and a significant increase in resistance rates was found for imipenem-resistant *A. baumannii* ($p = 0.003$) and third-generation cephalosporins-resistant Enterobacteriaceae ($p = 0.01$) isolates in this same period. **Conclusions:** Our results suggest that there is a link between antibiotics usage at institutional levels and resistant bacteria. The use of carbapenems was related to the high rate of resistance in *A. baumannii* and therefore a high consumption of imipenem/meropenem could play a major role in selective pressure exerted by antibiotics in *A. baumannii* strains.

Keywords: Antibiotic consumption. Intensive care unit. Ventilator-associated pneumonia. Antimicrobial resistance.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most-frequent intensive care unit (ICU)-acquired infection, occurring in 9.0-24% of patients intubated for longer than 48h. It is associated with increased morbidity, prolonged hospitalization, and increased healthcare costs[1].

Antimicrobial resistance is an increasing threat in hospitalized patients, and both mortality and morbidity from infection are greater when caused by antimicrobial-resistant bacteria[2,3]. Among these resistant bacteria, extended-spectrum cephalosporin-resistant Enterobacteriaceae, carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and ciprofloxacin-resistant Enterobacteriaceae and non-fermentative Gram-negative bacilli (NFGNB) are of great concern because antimicrobial therapy for infections due to these resistant pathogens remains a clinical dilemma[2,4]. Increases in the prevalence of these resistant pathogens are frequently related to the high selective pressure of antimicrobials commonly used in hospitalized patients, particularly extended-spectrum cephalosporins, β-lactam+β-lactamase inhibitor combinations, carbapenems, fluoroquinolones, and aminoglycosides[2,5].

Inappropriate empirical antimicrobial therapy is known to adversely affect outcome in pneumonia associated with a mechanical ventilator[6] and needs to be tailored to the institution's microbial ecology and the length of time the patient was in the hospital before pneumonia developed[4]. This question is frequent in Brazilian ICUs[7]. Multidrug-resistant organisms are far higher in ICUs in Latin America, Asia, Africa, and Europe than in U.S. ICUs[8].

This report aims to evaluate antimicrobial usage, incidence, etiology, and antimicrobial resistance trends for prominent nosocomial pathogens causing ventilator-associated pneumonia in a clinical-surgical ICU in a Brazilian university hospital.

METHODS

Hospital and study design

This work was performed at the Uberlândia Federal University Hospital Clinic (HC-UFU) which is a teaching hospital with 500 beds and a clinical-surgical ICU of adults with 15 beds.

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We conducted a cross-sectional study where the incidence density of major Gram-negative bacteria and *Staphylococcus aureus* causing VAP were expressed as the number of isolates per 1,000 patients-day (pd) per month in two different periods: A (May 2006 to April 2007) and B (September 2008 to August 2010). Only the first episode of VAP was considered for each patient. Endotracheal aspirate was collected by probe number 12 early in the morning by health professionals (physiotherapists and nurses) in charge of the procedure and transported in a sterile tube to the Microbiology Laboratory. Isolates were identified by conventional biochemical tests.

Definition of hospital ventilator-associated pneumonia

The patients were under a mechanical ventilator for a period ≥ 48h after being admitted to the ICU, with new and/or progressive radiological infiltrate, and at least under two of the following criteria: purulent sputum, temperature higher than 38.5ºC or lower than 35ºC, and leukocyte count higher than 10,000/μL with deviation to the left or lower than 3,000/μL; and positive quantitative culture of the endotracheal aspirate [count ≥ 10^6 colony-forming units/ml (CFU/ml)][9].

Antibiotic consumption

Data on antibiotic consumption were evaluated in period A and May 2009 to August 2010 and were expressed as the number of defined daily doses (DDDs)/1,000 patients-day (pd) for the main classes of antibiotics used in our ICU: glycopeptides (vancomycin and teicoplanin), carbapenems (imipenem, meropenem, and ertapenem), and extended-spectrum cephalosporins (ceftriaxone and cefepime).

There were no interventions or changes in the antimicrobial use policy in the institution between the two periods.

Trends in resistance

To determine the trend of resistance in major Gram-negative pathogens and *S. aureus* causing VAPs in ICU patients in the HC-UFU, data on the disk diffusion susceptibilities of these organisms were interpreted according to Clinical and Laboratory Standards Institute (CLSI) criteria[10], by the diameter of inhibition halo formed, using the following antimicrobial discs (Oxoid LTD., England): oxacillin (1ug), penicillin (10mg), erythromycin (15mg), cefoxitin (30mg), clindamycin (2mg), rifampicin (5mg), chloramphenicol (30mg), vancomycin (30mg), ciprofloxacin (5mg), gentamicin (10mg), cefepime (30mg), tetracycline (30mg) and sulphazotrim (25mg) for Gram-positive; imipenem (10mg), ciprofloxacin (5mg), ceftriaxone (30mg), gentamicin (10mg), piperacillin-tazobactam (100/10mg), polymyxin B (300u), cefepime (30mg), aztreonan (30mg), sulphazotrim (25mg) and tetracycline (30mg) for Gram-negative.

Statistical analysis

Analysis was performed by the Mann-Whitney test or Student T test after checking normality (Shapiro-Wilk and Lilliefors) and independence of the variables for comparisons between periods A and B.

Pearson's correlation coefficient was used to determine the relationship between antibiotic consumption and trends in resistance.

The results were considered statistically significant at a level of 5%. The epidemiological data were analyzed through the program Bioestat 5.0[11].

Ethical considerations

The Ethics Committee for Human Research of the Uberlândia Federal University (UFU) approved the project under number 364/08.

RESULTS

Etiology of ventilator-associated pneumonias

Periods A and B incidence density of major Gram-negative bacilli and *S. aureus* causing VAPs are shown in **Table 1** and **Figures 1** and **2**. For *A. baumannii* and members of the Enterobacteriaceae family, 5.27- and 3.06-fold increases in VAPs were nocted, respectively. On the other hand, there was a 2.0-fold decrease in the incidence density of *S. aureus* causing VAPs. Among the Gram-negative bacilli isolates, trends of increase in incidence density were significant ($p \leq 0.05$) just among *A. baumannii* and members of the Enterobacteriaceae family causing VAPs (**Table 1**). Other non-fermenters, except *P. aeruginosa* and *A. baumannii*, were observed only in period B (1.62 isolates/1,000 patient-days).

TABLE 1 - Incidence density of microorganisms isolates from ventilator-associated pneumonia (isolates/1,000 patient-days) in two different periods in the adult ICU at UFU-HC.

Pathogen	Period A	Period B	p*
	mean (SD) median	mean (SD) median	
Staphylococcus aureus	4.23 (4.27) 3.16	2.11 (1.98) 2.15	0.21
ORSA	2.40 (3.35) 1.07	0.36 (0.83) 0.0	0.07
OSSA	1.82 (1.80) 2.15	1.74 (2.04) 2.15	0.80
Pseudomonas aeruginosa	4.36 (3.90) 2.30	5.02 (3.45) 4.30	0.43
imipenem-resistant	2.72 (3.09) 2.15	2.28 (2.09) 2.15	0.85
Acinetobacter baumannii	0.73 (1.44) 0.0	3.85 (3.73) 2.18	0.008
imipenem-resistant	0.18 (0.62) 0.0	3.12 (3.41) 2.15	0.003
Enterobacteriaceae	0.90 (1.94) 0.0	2.75 (2.45) 2.15	0.02
resistant to third- generation cephalosporins	0.18 (0.62) 0.0	1.54 (1.63) 2.15	0.01

ICU: intensive care unit; **UFU-HC:** Uberlândia Federal University-Hospital Clinic; **SD:** standard deviation**; ORSA**: oxacillin-resistant *Staphylococcus aureus*; **OSSA:** oxacillin-sensitive *Staphylococcus aureus.* *Mann-Whitney test.

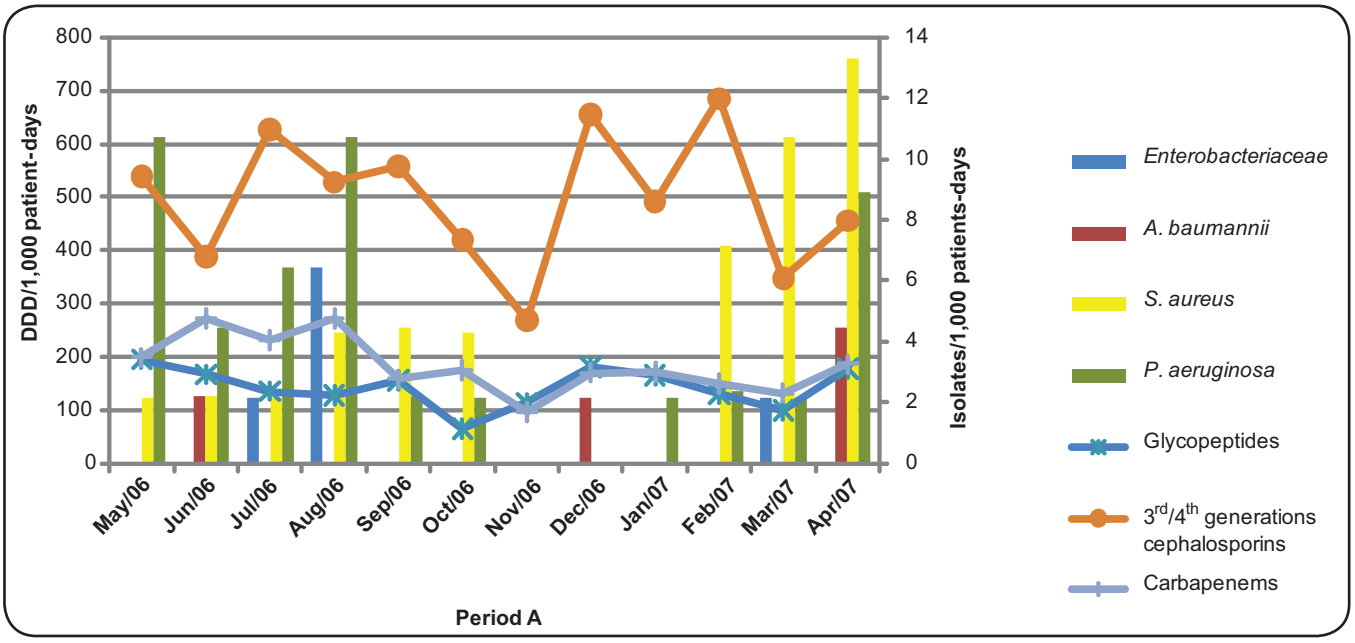

FIGURE 1 - Relationship between incidence density of microorganisms isolated from ventilator-associated pneumonia (isolates/1,000 patient-days) and density of use of antimicrobials in defined daily doses (DDD/1,000 patient-days) in the adult ICU at UFU-HC for period A.

DDD: defined Daily Doses; **ICU:** intensive care unit; **UFU-HC:** Uberlândia Federal University-Hospital Clinic; ***A. baumannii:*** *Acinetobacter baumannii;* ***S. aureus****: Staphylococcus aureus;* ***P. aeruginosa:*** *Pseudomonas aeruginosa.*

Period antibiotic consumption

Table 2 shows the consumption of three classes of antibiotics in both periods. There was no significant variation in the consumption of broad-spectrum cephalosporins as opposed to glycopeptides (1.88-fold) and carbapenems (1.43-fold) when comparing periods A and B (**Table 2**, **Figures 1** and **2**).

In period A, the density of use of third- or fourth-generation cephalosporins grew in respect to glycopeptides and carbapenems **(Table 2)**. In period B, the consumption of antimicrobials was higher than in period A for all classes evaluated, with emphasis on higher-density use of broad-spectrum cephalosporins **(Table 2)**.

Relationship between antibiotic consumption and resistance

The overall rates of resistance to imipenem were 25% and 80.9% in *A. baumannii* and 62.5% and 45.5% in *P. aeruginosa* in periods A and B, respectively. For *S. aureus*, overall rates of resistance to oxacillin were 56.5% and 17.4% in periods A and B, respectively. Regarding third-generation cephalosporins, the overall rates of resistance were 20% and 56.7% in Enterobacteriaceae isolates in periods A and B, respectively. **Table 1** shows the trends of resistance among Gram-negative pathogens and *S. aureus*.

In period A, only the consumption of carbapenems showed a significant correlation (Pearson r = 0.66/p=0.02) with the occurrence of VAPs by *P. aeruginosa*, especially with strains resistant to imipenem (Pearson r=0.70/p=0.01) **(Figure 3)**. The rates of antibiotic resistance of other organisms were not correlated with the consumption of antimicrobials evaluated in the Pearson correlation test.

A significant increase in resistance rates in period B was found for imipenem-resistant *A. baumannii* and third-generation cephalosporins-resistant Enterobacteriaceae isolates. This same period showed a significant increase in consumption of carbapenems, and the use of broad-spectrum cephalosporins was still higher than during period A, but there was no correlation with resistance rates of these microorganisms in the Pearson correlation test.

Figures 1 and **2** show the relationship between consumption of antibiotics and the etiology of VAPs.

TABLE 2 - Average consumption of antibiotics in DDDs per 1,000 patient-days of glycopeptides, carbapenems, and extended-spectrum cephalosporins in adult ICU at UFU-HC in two different periods.

Antimicrobial	Period A	Period B	p*
	mean (SD) median	mean (SD) median	
Glycopeptides	142.98 (37.93) 145.68	269.56 (82.12) 237.02	<0.0001
Extended-spectrum cephalosporins	496.87 (127.03) 510.36	551.26 (156.34) 517.79	0.33
Carbapenems	184.29 (37.93) 179.62	263.57 (81.0) 271.80	0.007

DDDs: defined daily doses; **ICU:** intensive care unit; **UFU-HC:** Uberlândia Federal University-Hospital Clinic; **SD:** standard deviation**;** *Student T test.

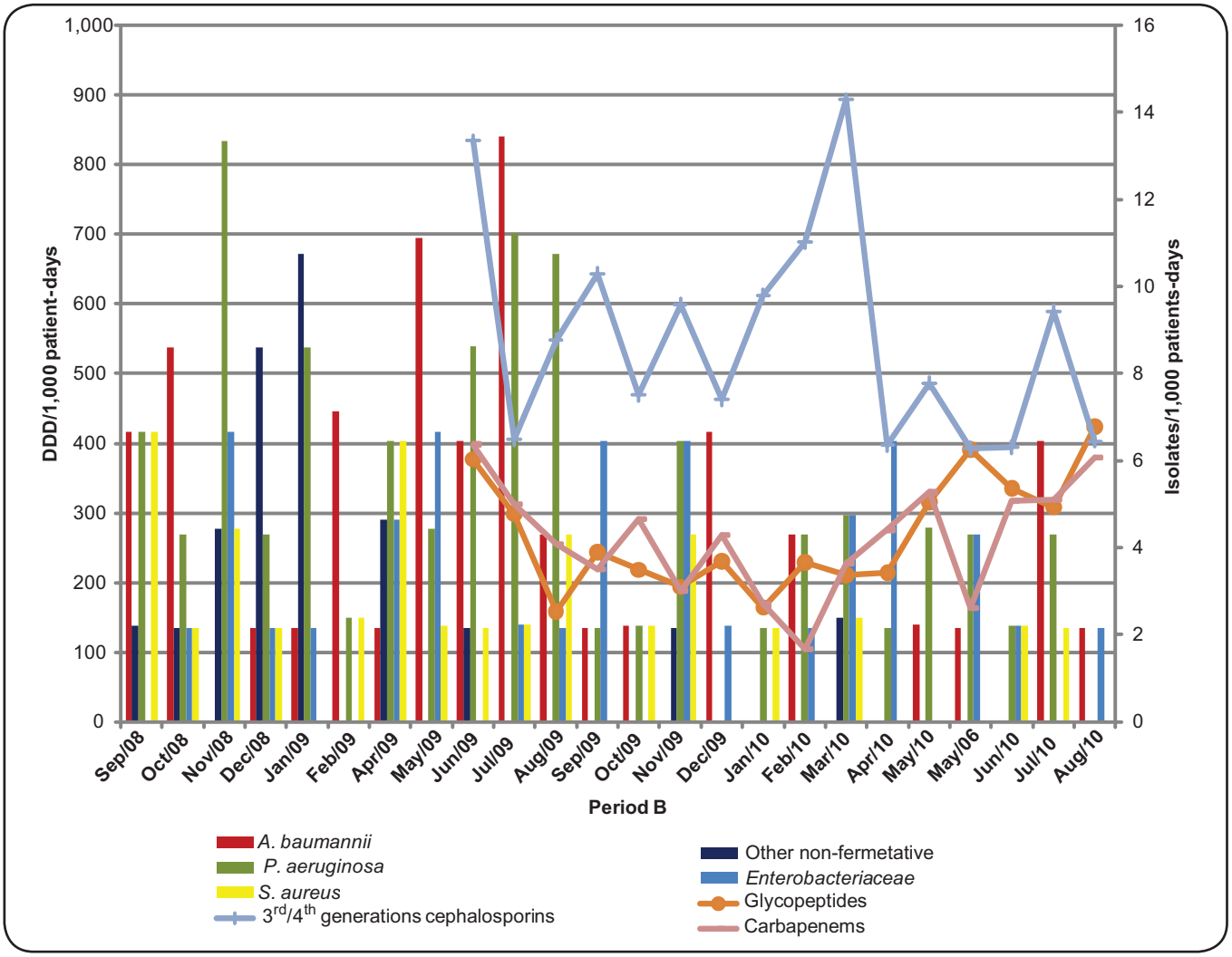

FIGURE 2 - Relationship between incidence density of microorganisms isolated from ventilator-associated pneumonia (isolates/1,000 patient-days) and density of use of antimicrobials in defined daily doses (DDD/1,000 patient-days) in the adult ICU at UFU-HC for period B.

DDD: defined daily doses; **ICU:** intensive care unit; **UFU-HC:** Uberlândia Federal University-Hospital Clinic; ***A. baumannii:*** *Acinetobacter baumannii;* ***S. aureus****: Staphylococcus aureus;* ***P. aeruginosa:*** *Pseudomonas aeruginosa.*

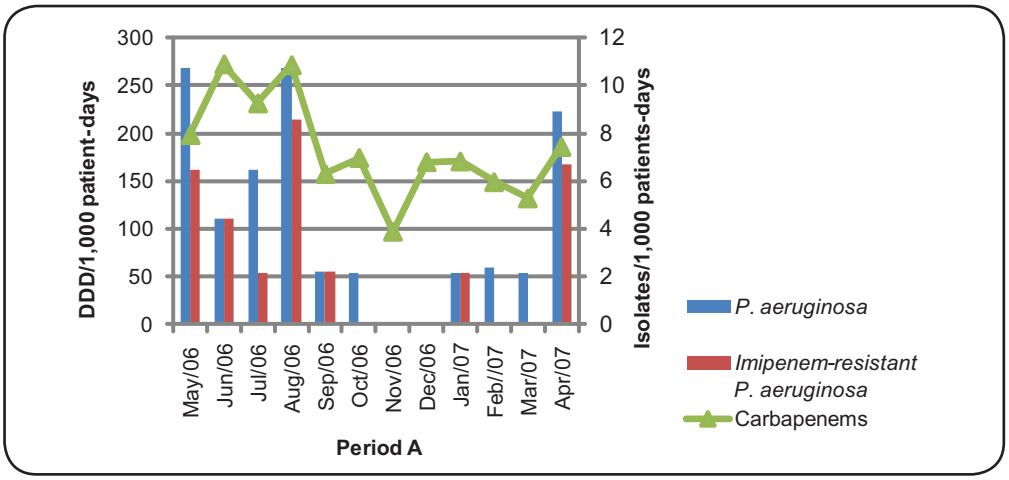

FIGURE 3 - Relationship between incidence density of* Pseudomonas aeruginosa *isolated from ventilator-associated pneumonia (isolates/1,000 patient-days) susceptible (Pearson r = 0.66/p = 0.02) or resistant (Pearson r = 0.70/p = 0.01) to imipenem and density of use of Carbapenems in defined daily doses (DDD/1,000 patient-days) in the adult ICU at UFU-HC for period A.

DDD: defined daily doses; **ICU:** intensive care unit; **UFU-HC:** Uberlândia Federal University-Hospital Clinic; ***A. baumannii:*** *Acinetobacter baumannii;* ***S. aureus****: Staphylococcus aureus;* ***P. aeruginosa:*** *Pseudomonas aeruginosa.*

DISCUSSION

Regarding the etiology of VAPs, we observed a decrease in the frequency in VAPs caused by *S. aureus* and an increase in the frequency of VAPs by Gram-negative bacilli in period B. Changes in the frequency of these pathogens may be due to multiple factors (e.g., implementation of targeted surveillance, multidrug-resistant organism outbreaks, active surveillance, etc.) besides the agents may fluctuate over time[12]. Several studies found that prior administration of antibiotics can alter the distribution of microbial pathogens isolated from patients with VAP. For example, in a prospective study of 129 episodes of VAP, prior use of antibiotics significantly decreased the incidence of VAP caused by Gram-positive cocci or *Haemophilus influenzae* but increased the rate of those caused by *P. aeruginosa*[13]. In our ICU, we observed a decrease in rates of oxacillin-resistant *Staphylococcus aureus* (ORSA) despite the highest use of glycopeptides for empirical antimicrobial treatment of infections in the period B ($p < 0.0001$). In the UK hospitals, the introduction of mandatory surveillance and the use of a national *clean your hands* campaign resulted in a 50% reduction of ORSA bacteraemia[14]. In U.S. hospitals, ORSA central line-associated bloodstream infections (BSI) incidence also declined 50% or more in recent years in all major adult ICU types, as reported by the Centers for Disease Control and Prevention (CDC)[15]. These observations are consistent with reports of successful prevention efforts by health care teams that implemented programs designed to improve care practices[15]. Such decreases have been evident in other developed countries with national health care-associated infection surveillance and prevention efforts[15-17].

The incidence of VAP due to major Gram-negative bacteria increased over time, but *P. aeruginosa* remained the most-prevalent bacteria, 40% and 32.4% in periods A and B, respectively, as represented in other South American ICUs[18]. In our study, 62.5% and 45.5% of *P. aeruginosa* isolates were resistant to imipenem in periods A and B, respectively. These rates are high when compared with those in other studies[8,19].

Acinetobacter baumannii is another important cause of nosocomial infections in many hospitals, which is difficult to both control and treat because of its prolonged environmental survival and its ability to develop resistance to multiple antimicrobial agents[20,21]. *A. baumannii* pneumonia occurs predominantly in selected subjects with various risk factors such as mechanical ventilator, residence in an ICU, and prior antibiotic use mainly of broad-spectrum drugs such as third-generation cephalosporins and carbapenems[22]. In our study, *A. baumannii* rates increased in period B ($p = 0.008$), and this bacteria was the second-most-frequently isolated in this period when the use of broad-spectrum cephalosporins and carbapenems were higher than in period A ($p = 0.33$ and 0.007, respectively) and extremely high when compared to rates of use in U.S.[23] (37.8 and 144.1 DDDs/1,000pd for carbapenems and 3rd generation cephalosporins, respectively) and German[5] ICUs (83.7 and 109.5 DDDs/1,000pd for carbapenems and 3rd generation cephalosporins, respectively). *A. baumannii* appears to have a propensity for developing antimicrobial resistance extremely rapidly. Moreover, this resistance is multiple, causing serious therapeutic problems[20]. Carbapenems are usually the antibiotics of choice for treating serious infections caused by this microorganism. However, reports of imipenem-resistant *A. baumannii* strains have been rising steadily during the past few year, and these isolates are often multidrug-resistant[20,21,24]. Although these multiresistant *A. baumannii* strains may still retain susceptibility to polymyxins (i.e., colistin and polymyxin B), sulbactam and possibly tigecycline pan-resistant isolates that are resistant to all available drugs are now reported[24]. In our study, 25% and 80.9% of the isolates of *A. baumannii* were resistant to carbapenems in periods A and B, respectively ($p = 0.003$).

Gram-negative bacilli of the Enterobacteriaceae family are common causes of health-care-associated pneumonias[25]. Emerging resistance in this microorganism is a significant problem that requires immediate attention, and the increasing prevalence of multidrug-resistance Enterobacteriaceae challenges the use of third-generation cephalosporins for empirical treatment of nosocomial infections[25,26]. In our study, the rates of Enterobacteriaceae isolates increased in period B ($p = 0.02$) and were the third-most-isolated pathogen during this period; 20.0% and 56.7% of these microorganisms were resistant to third-generation cephalosporins in periods A and B, respectively ($p = 0.01$). The emergence of extended-spectrum β-lactamases (ESBLs) necessitated the increased use of carbapenems, but this increased use of *drugs of last resort* may be contributing to the emergence of multidrug-resistant non-fermentative Gram-negative bacilli[27,28].

The root causes of the rapid emergence and dissemination of drug-resistant bacteria in hospitals are multifactorial[2,29,30], including mainly the high selective pressure that results from inappropriate and widespread use of antimicrobial agents particularly in ICUs; cross transmission from patient to patient owing to inconsistent application of appropriate infection control measures; clonal spreading of resistant bacteria and horizontal transfer of resistance genes; and a complex relationship between resistance and use of a variety of antimicrobials[2,29,31]. However, increasing resistance may further drive increased consumption of several so-called *last-line* antimicrobial agents[2]. In this study, the increase in the incidence of VAP due to multidrug-resistant *A. baumannii* and third-generation cephalosporins-resistant Enterobacteriaceae resulted in an increase of carbapenems. The increased use of these agents was associated with an increase in the incidence of VAPs due to carbapenem-resistant *A. baumannii.*

Our results suggest a link between antibiotics usage at institutional levels and resistant bacteria. The emergence of *P. aeruginosa* in our ICU necessitated the increased use of carbapenems, which may contribute to the emergence of multidrug-resistant non-fermentative Gram-negative bacilli, mainly *A. baumannii*. Antibiotic resistance is an inevitable consequence of inappropriate antibiotic use, which is more likely in units with high prevalence of multidrug-resistant microorganisms.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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