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Research Article

Prevalence and determinants of antimicrobial resistance of gram-negative bacteria in intensive care unit

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ABSTRACT

Antimicrobial resistance (AMR) has become a concerning health issue worldwide, and this resistance leads to poor treatment outcomes and high mortality, especially, AMR of NP in ICU. To determine the reality of AMR and find the factors related to AMR of NP in the ICU. We performed a cross-sectional study in the ICU Department from July 2015 to July 2019. We calculated the incidence of the degree of multidrug-resistant strains and the percentages of factors related to AMR. Data management and analysis were performed by SPSS version 22.0. Of the initial observation of 281 patients, all participants had NP due to gram-negative bacteria; 91 (32.4%) were early-onset and 190 (67.6%) were lately-onset NP. Out of all pathogens examined, above 80% were resistant to quinolone, carbapenem, and cephalosporin. Moreover, multiple drug resistance in bacteria was about 87.5%. Furthermore, bacteria, changed anti-biotics have been significantly associated with the multi-resistance of bacteria. Besides, the increase in antibiotic use, especially ciprofloxacin and imipenem, is also related to antibiotic resistance. These results show that the resistance to quinolones, carbapenem, and cephalosporin is high in the ICU, with rates exceeding 80%. Furthermore, the bacteria, change of antibiotics, and the increasing use of antibiotics have been significantly associated with multiple antibiotic resistance.

Keywords:
Antimicrobial resistance, Gram-negative bacteria, Intensive care unit

1. INTRODUCTION

Antimicrobial resistance (AMR) has become a concerning health issue worldwide, and this resistance leads to poor treatment outcomes and even death. In 2014, about two million Americans were admitted with hospital-acquired infections, accounting for 99,000 deaths, the majority of which were caused by antimicrobial-resistant pathogens. In addition, the length of stays in hospitals with antibiotic-resistant infections was extended from 6.4 to 12.7 days, so antibiotic-resistant infections also caused a financial burden on the healthcare system and population. In a study about bacteriophage therapy, the medical cost for an antibiotic-resistant infection reaches $20 billion for the total economic burden. As a result, antibiotic resistance is the most challenging public health and economic problem nowadays[1].

In pathogens of nosocomial infections, the prevalence of gram-negative bacteria was much higher than that of gram-positive bacteria. According to the study, in Iran, 77.9% of gram-negative and 22.1% of gram-positive were found, and *Escherichia coli* reached 839/1394 (59.6%), followed by *Klebsiella pneumoniae* with 139 (9.9%), *Pseudomonas aeruginosa* 71 (5.1%), *Enterobacter spp.* 31 (2.2%), *Acinetobacter baumannii* 30 (2.15%), and *Klebsiella oxytoca* 18 (1.2%)[2]. Moreover, the major causes of nosocomial pneumonia (NP) were *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa*[3].

NP is a serious bacterial disease, so the guidelines suggest using broad-spectrum antibiotics and combining antibiotics as soon as it is diagnosed. In 2016, the Infectious Diseases Society of America and the American Thoracic Society (ATS/IDSA) recommended using piperacillin, ceftazidime, ceftriaxone or a carbapenem plus a fluoroquinolone, or amikacin as initial therapy for nosocomial pneumonia. Research about NP showed that

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empirical antibiotic therapy used for ventilator-associated pneumonia (VAP) included cephalosporins (46.5%), penicillins (43%), carbapenems (35.9%), fluoroquinolones (18.1%), and glycopeptides (14.6%) whereas penicillins (47.3%), cephalosporins (42.1%), fluoroquinolones (27.5%), carbapenems (23.2%), and glycopeptides (12.2%) were used for hospital-acquired pneumonia (HAP)[4]. However, a study discovered that the frequencies of resistances were 445/493 (90.1%) of ceftazidime, 406/559 (79.8%) of cefepime, 400/532 (75.2%) of imipenem, 335/497 (67.5%) of meropenem, and other study showed 73/75 (97.3%) of quinolone (ciprofloxacin and levofloxacin), and (17/75) 22.7% of aminoglycoside (gentamycin and amikacin)[5-6]. Furthermore, there was a significant relationship between antibiotic prescriptions and AMR rates in gram-negative bacteria[7].

The Centers for Disease Control and Prevention (CDC) have given three reasons why Vietnam has significantly contributed to antimicrobial resistance. First, laboratories often lacked the resources or trained staff to reliably detect several types of resistance. Second, overcrowded, understaffed hospitals with insufficient infection control can allow the spread of resistant bacteria. Third, antibiotics are often overprescribed or are the incorrect dose or duration[8].

In recent years, increasing AMR has been a big challenge to the health system in Vietnam. This issue's risk factors and outcomes have always been major subjects for infectious disease projects. Furthermore, NP in the intensive care unit (ICU) has been the most severe hospital-acquired infection and antibiotic therapy has been a factor in deciding the patient's survival. Therefore, the objective of this study is to discover the reality and the factors related to antimicrobial resistance of nosocomial pneumonia in the ICU.

2. MATERIAL AND METHODS

2.1. Study population

Materials: This cross-sectional research was conducted in the Intensive Care Unit Department of a southern Vietnam hospital from July 2015 to July 2019.

Inclusion criteria: Adult patients (at least 18 years old) were diagnosed with first-ever nosocomial pneumonia for inclusion in the study.

Exclusion criteria: Patients were diagnosed with acute pulmonary edema, unavailable culture-antibiogram, or acid-fast bacillus test positive.

2.2. Methods

Study design: The cross-sectional study was designed to address two questions: (i) the reality of AMR of NP in ICU (ii) the factors related to AMR of NP in the ICU.

Sample size: 298 participants were obtained over four years.

Data collection: As soon as patients were diagnosed with NP, the dataset of patients was conducted from medical records. The baseline information was collected from all patients, including age as well as gender, and calculated for quick Sequential Organ Failure Assessment (qSOFA) scores. The time of onset of pneumonia and procedure of antibiotic usage was also recorded. The risk factors and the levels of antimicrobial resistance, including non-Multidrug-resistant (non-MDR), Multidrug-resistant (MDR) were evaluated for all participants.

As for the first question, we calculated the incidence of the degree of multidrug-resistant strains, including non-MDR, MDR which were identified by the European Centre for Disease Prevention and Control (ECDC) and CDC criteria[17]. Moreover, we determined the prevalence of resistance to types of antibiotics by analyzing datasets from the antibiogram. As for the second question, we calculated the percentages of factors between the groups by age, gender, ventilated pneumonia, time of onset NP, bacteria, prescribed antibiotics, change of initial antibiotics, and Quick Sequential Organ Failure Assessment (qSOFA) score. Utilized empiric antibiotics included imipenem, meropenem, ertapenem, ceftazidime, ceftriaxone, cefepime, piperacillin-tazobactam, colistin, levofloxacin, ciprofloxacin, amikacin, respectively. Vancomycin, teicoplanin, linezolid, metronidazole, and clindamycin were added as supplemental medications. A total of 521 antibiotics were prescribed for 281 patients, so the distribution of antibiotic use was calculated by the number of a type of prescribed antibiotics per 521. Then, we analyzed univariate and multivariate data to find associations between the factors and AMR.

Ethical approval for this study was obtained from Can tho University of Medicine and Pharmacy, Vietnam with 1530/QD-DHYDCT in June 2015. Kirby Bauer disc diffusion method was used to test the antibiotic susceptibility of bacterial strains in accordance with Clinical Laboratory Standard Institute (CLSI) guidelines[9-10]. We were evaluating the appropriateness of empiric antibiotic therapy based on the guidelines of ATS/IDSA 2016[11].

Variables: NP was defined as pneumonia occurring more than 48 hours after hospitalization, with new or progressive pulmonary infiltrates on chest X-ray and at least one of the following criteria: leukocyte count greater than 12,000/mm^3 or less than 4,000/mm^3 or temperature above 38.3°C, as well as at least the two clinical criteria: purulent sputum; cough or dyspnea; declining oxygenation or increased oxygen-requirement; or need for respiratory assistance. Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP) were the two types of NP. HAP was defined as an episode of NP that did not require mechanical ventilation for at least 48 hours. VAP was defined as pneumonia that occurred more than 48 hours after intubation and ventilation[12].

Quick Sequential Organ Failure Assessment (qSOFA)

are system scores to predict mortality in patients with sepsis. qSOFA≥2 is considered high risk for sepsis[13].

Early-onset NP is characterized as occurring within the four days of admission, and late-onset NP is defined as occurring after the four days of admission[14].

A change of antibiotics was defined as adding or switching to another antibiotic with a broader or narrower antibacterial spectrum after the results of antimicrobial susceptibility testing[15].

The bacteriologic diagnosis was defined as bacterial growth of 10^5 colony-forming units/ml or more in tracheal aspirates or 10^4 colony-forming units/ml or more in bronchoalveolar lavage[16].

Non-MDR was defined as susceptibility from three or more antimicrobial groups.

MDR bacteria was defined as acquired resistance to at least one drug from three or more antimicrobial groups[17].

Data analysis: Dataset was analyzed by using SPSS version 22.0. The Chi-square test or Fisher test and logistic regression modeling were used to determine statistically significant differences in values (age, gender, ventilate invasion, antibiotic essentials, qSOFA score, microbiology agents, and antimicrobial resistance) among

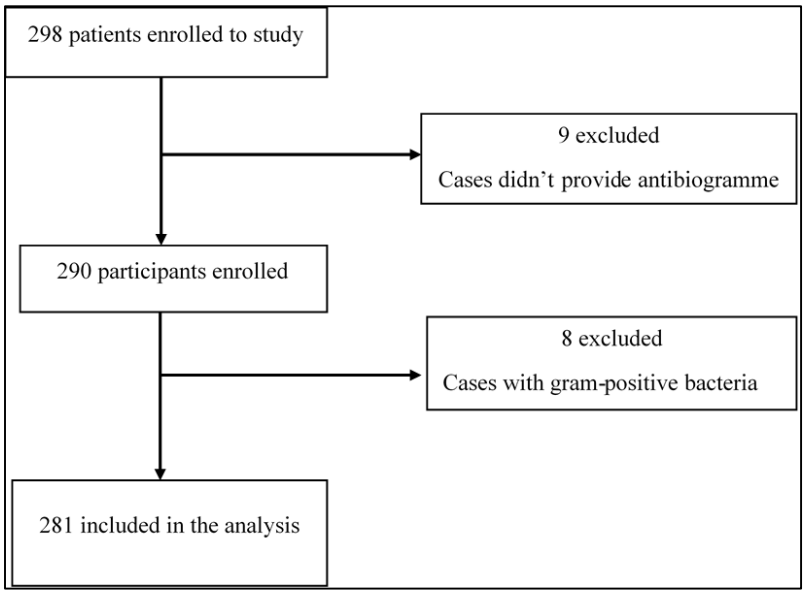

Figure 1. Flow diagram of the study.

Table 1. Demographic data and baseline clinical characteristics (N=281).

	n (%)
Age*	70.5 ± 15
Male	161 (57.3)
Classification of pneumonia according to time of onset	
Early-onset	91 (32.4)
Late-onset	190 (67.6)
Mechanical ventilation	
Yes	163 (58.0)
No	118 (42.0)
qSOFA score of ≥2 points	
Yes	131 (46.6)
No	150 (53.4)
Department admission	
Emergency	138 (49.1)
Respiratory	43 (15.3)
Others	100 (35.6)
Antibiotic therapy	
Monotherapy	41 (14.6)
Combination therapy	240 (85.4)
Degree of antimicrobial resistance	
Non-MDR	35 (12.5)
MDR	246 (87.5)

*mean±SD

the cases. The outcome is non-multidrug-resistant and multidrug-resistant bacteria. The analyses were performed on the whole sample. The statistical significance variations were set at $p<0.05$. Furthermore, the figures were created by using Microsoft Excel 2010.

3. RESULTS

3.1. Basic characteristics of participants

From July 2015 to July 2019, 298 participants were obtained in Can Tho, and we included 281 patients in the study (Figure 1). All patients were infected with gram-negative bacteria and were collected data for empiric antibiotic treatment and antibiogram (Table 1).

3.2. Antimicrobial resistance

The overall rate of antimicrobial resistance was 87.5%, with the highest of *A. baumannii* at 59.4% (Figure 3). More than 80% of tested strains resisted carbapenems, cephalosporins, and quinolones (Figure 4).

3.3. Determinants of antibiotic resistance

The proportion of *A. baumannii* was 177 (63%), which was the most common pathogen of NP in ICU (Figure 2).

During the study, the patients were treated with hospital-based guidelines on the recommendation of ATS/IDSA 2005 and 2016. For empiric antibiotics, carbapenem was the highest with 74%, followed by

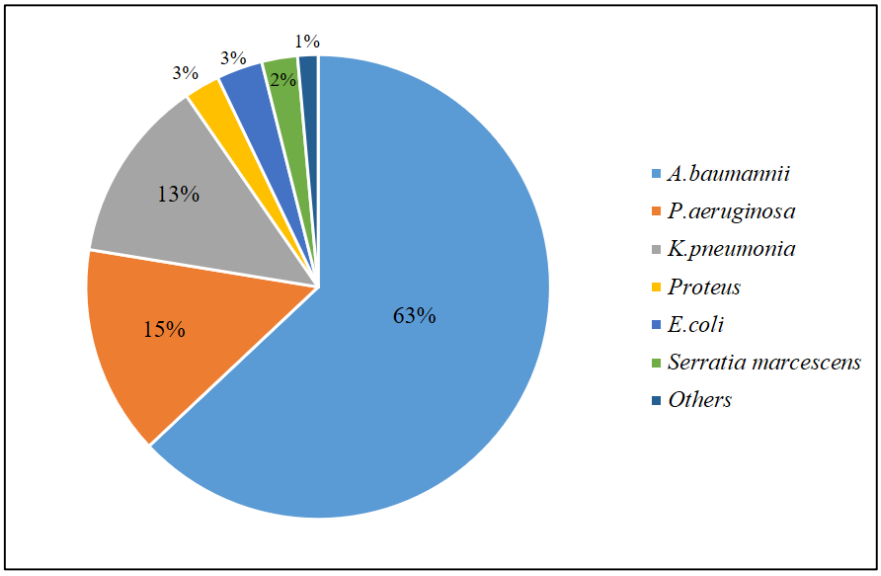

Figure 2. Proportions of pathogens identified in samples from nosocomial pneumonia patients.

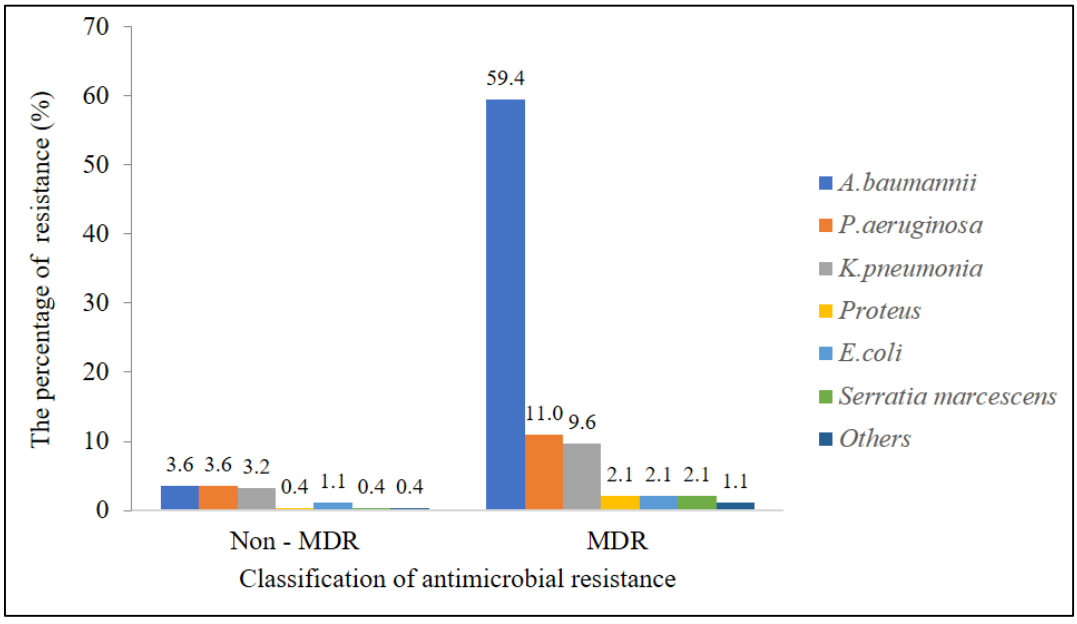

Figure 3. Prevalence of antimicrobial resistance in particular pathogens grouped by degree.
Abbreviations: non-MDR, non-Multidrug-resistant; MDR, Multidrug-resistant

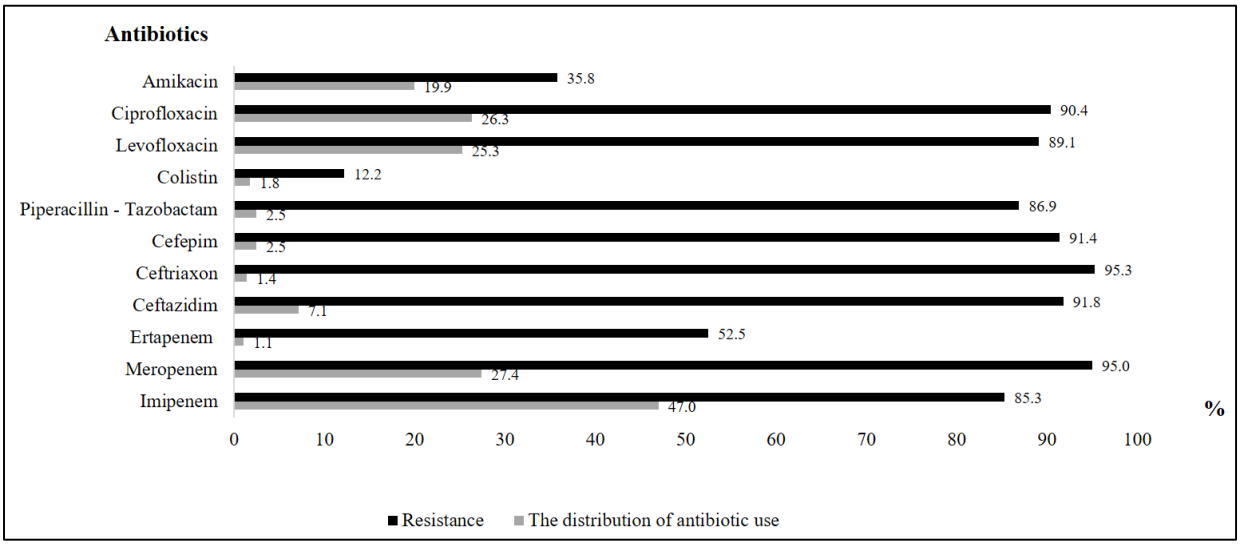

Figure 4. Association between use and resistance to imipenem and ciprofloxacin in the two groups (from 2015 to 2017 and from 2017 to 2019).

quinolones (54%) and amikacin (20%) (Figure 4). Most remarkably, 189 (67.3%) of 281 patients were exposed to antibiotics with antipseudomonal activity, and 21 (7.5%) combined gram-positive antibiotics with MRSA activity. Besides, 71 (25.3%) of 281 cases were prescribed with a combination between cefoperazone or ceftriaxone and quinolones or amikacin or clindamycin (Table 2).

We found a significant association between the use and resistance of imipenem and ciprofloxacin. We compared the use and resistance of ciprofloxacin and imipenem during 2 periods: from 2015 to 2017 and from 2017 to 2019. The use of ciprofloxacin increased by 15.6%, and the resistance of ciprofloxacin also increased by 11.1%. Besides, the use of imipenem increased by 41.8%, and the resistance of imipenem also increased by 27.4% (p<0.05) (Figure 5). Little differences were measured between the use and the resistance of meropenem, levofloxacin, and amikacin between the two groups (Figure 4).

The estimates did not change substantially after the adjustment for age ≥65, gender, onset time of NP, and departments before the ICU was admitted (Table 3). According to the analysis, changing antibiotics, and pathogens significantly increased the risk of antibiotic resistance (p<0.05).

4. DISCUSSION

The most common resistant pathogens of nosocomial pneumonia were *A. baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. A prospective study of the 156 enrolling centers from various regions worldwide and 73 hospitals in 10 Asian countries was conducted from 2008-2009; these were the most frequent four pathogens in HAP and VAP. However, these bacteria were distributed differently in each country: *A. baumannii* (China, Thailand, Malaysia, and Iran), *P. aeruginosa* (Hong Kong, Taiwan, Spanish, and United States), and *K. pneumoniae* (Philippines, Indonesia, and Singapore). Moreover, the levels of antibiotic resistance were also different from bacterial isolates; for example, *A. baumannii* and *P. aeruginosa*, *K. pneumonia* was MDR[16,18-19]. Two mechanisms can cause multidrug resistance in bacteria. First, these bacteria might accumulate multiple genes, each coding for resistance to a single drug. This type of resistance occurs typically on resistance plasmids. Second, the type of

Table 2. Empiric treatment options of nosocomial pneumonia (N=281).

β-lactam-based agents	Non-β-lactam-based agents	n (%)
Gram-Negative antibiotics with antipseudomonal activity		
Carbapenem	Quinolone	112 (39.9)
	Amikacin	45 (16.0)
	Colistin	2 (0.7)
Cephalosporin	Quinolone	22 (7.8)
	Amikacin	5 (1.9)
Piperacillin-Tazobactam	Quinolone	2 (0.7)
	Amikacin	1 (0.4)
Gram-positive antibiotics with MRSA activity		
Carbapenem/Cephalosporin/	Vancomycin	8 (2.9)
Piperacillin-Tazobactam	Linezolid	13 (4.6)
Others		71 (25.8)

Table 3. Factors influence antimicrobial resistance (N=281).

	Non MDR n (%)	MDR n (%)	p-value
Sex			
Male	19 (54.3)	142 (57.7)	0.700
Female	16 (45.7)	104 (42.3)	
Age >=65			
No	11 (31.4)	74 (30.1)	0.871
Yes	24 (68.6)	172 (69.9)	
Pathogens[b]			
A.baumannii	10 (28.6)	167 (67.9)	<0.001
P.aeruginosa	10 (28.6)	31 (12.6)	
K.pneumoniae	9 (25.7)	27 (11.0)	
Proteus	1 (2.9)	6 (2.4)	
E.coli	3 (8.6)	6 (2.4)	
Serratia marcescens	1 (2.9)	6 (2.4)	
Bukhoderia cepacia	0 (0.0)	1 (0.4)	
Others	1 (2.9)	2 (0.8)	
Change antibiotic			
No	22 (62.9)	211 (85.8)	0.001
Yes	13 (37.1)	35 (14.2)	
qSOFA >=2			
No	24 (68.6)	126 (51.2)	0.054
Yes	11 (31.4)	120 (48.8)	
Department before admitted to ICU			
Emergency care	21 (60.0)	117 (47.6)	0.184
Respiratory	2 (5.7)	41 (16.7)	
Others	12 (34.3)	88 (35.8)	
Classification of pneumonia according to time of onset			
Early-onset	16 (45.7)	75 (30.5)	0.072
Late-onset	19 (54.3)	171 (69.5)	
Mechanical ventilation			
Yes	22 (62.9)	141 (57.3)	0.534
No	13 (37.1)	105 (42.6)	

[a] Using Chi-square test if other tests were not mentioned.
[b] Using Fisher's exact test.

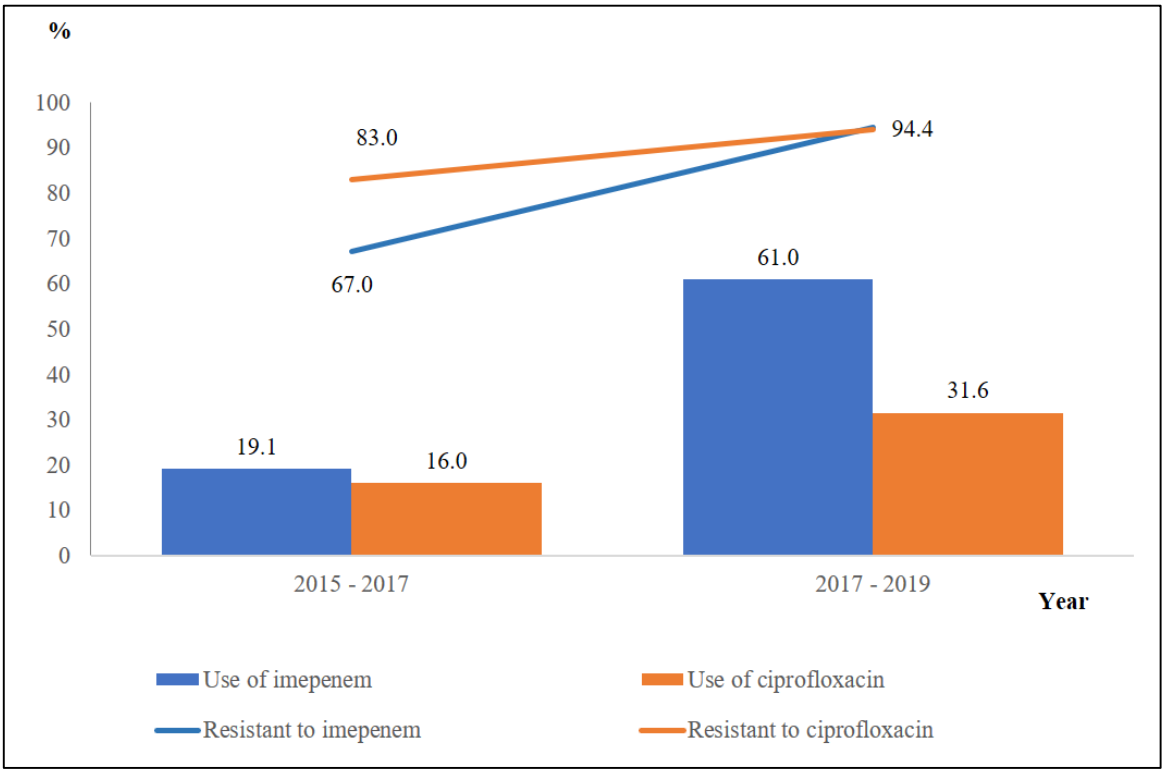

Figure 5. Proportions of antibiotic consumption and resistance.

resistance, namely multidrug resistance, might also occur by the increased expression of genes that code for multi-drug efflux pumps, enzymatic inactivation, and changes in the structure of the target[4].

A positive correlation was found between antibiotic use and the resistance rate of gram-negative pathogens. In our study, the increasing use of ciprofloxacin and imipenem in recent years was associated with increased resistance to these antibiotics, similar to other research results[7,20]. Increasing antibiotic consumption, especially broad-spectrum antibiotics and antibiotics against MDR pathogens, may increase selective pressure on certain classes of antibiotics in pathogens. Concerning the previous studies, the consumption of fluoroquinolones has probably caused the resistance of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *A.baumannii* to ciprofloxacin. Furthermore, perhaps the consumption of carbapenems has increased the resistance of *A. baumannii* and *P. aeruginosa* to imipenem[21]. Several authors gave the antibiotic cycling term to mean withdrawal of an antibiotic from use for a defined period to reduce antibiotic pressure as a stimulus for antibiotic resistance[15].

The use of carbapenem, ciprofloxacin, and levofloxacin needs to be warranted in Vietnam. Carbapenem was used more than the recommendations for treating nosocomial pneumonia by the Infectious Diseases Society of America and the American Thoracic Society in 2016. This guideline suggests using β-Lactam drugs for negative gram bacteria, including piperacillin-tazobactam, cefepime, ceftazidime, and carbapenem as initial empirical antibiotic therapy. According to our findings, imipenem and meropenem were chosen in above 70% of cases, and the resistance to these antibiotics was higher than in other Asian countries[18].

Changing antibiotics can promote the increase of antibiotic resistance. In our study, the rate of changing antibiotics was higher than those of several Asia countries. Changing antibiotics often occurred after getting the results of the antibiogram. Increasing antibiotic resistance, underlying diseases, and severity of disease in ICU patients are a large bargain for choosing initial antibiotics and also are caused for changing antibiotics in these patients. When the resistance to various antibiotics within a class is caused by the stepwise accumulation of mutations, it can be difficult to replace an antibiotic that is losing effectiveness due to resistance with a new drug from the same class. Such replacement may improve treatment success in the short term, but it also promotes acquired resistance and the "outbreak" of infection with multidrug-resistant organisms[22].

Antibiotic resistance has become one of the significant challenges and global burdens. Antibiotic resistance is the cause of prolonged hospital stays, treatment costs, and mortality[1,3]. Based on the results of our research, we give the following recommendations: 1) provide information on the prevalence of antibiotic resistance to choose appropriate empiric antibiotics; 2) design mixing and cycling antibiotics; 3) keep in private and isolated rooms in the infected cases with multiple resistance bacteria.

The strengths of our study were the collected data during the four years. All of the patients had antibiograms related to access the effectiveness of using antibiotics and antimicrobial resistance of NP in the ICU setting. Sputum analysis is essential in the evaluation and management of lower respiratory infections. In this study, all sputum specimens were collected and determined when the bacteria count was over 10^4/cfu. They were similar to those found in other Asian countries these bacteria were the primary pathogens for nosocomial pneumonia. Furthermore, our study was based on the CLSI standard, one of the two most commonly used methodologies worldwide for antimicrobial susceptibility testing and recommended in the World Health Organization's Global Antimicrobial Resistance Surveillance System[10]. Therefore, this study aims to highlight the usage of antibiotics and AMR in a region of Vietnam, which helps determine the current issue and find a better resolution for treatment and prevention.

4.1. Study limitations

The weakness of our study was the absence of data for positive gram bacteria in nosocomial pneumonia, and we didn't have enough data to certainly determine the increased use which will lead to the increased resistance of all antibiotics. Furthermore, the proportion of non-MDR bacteria is much lower than multidrug-resistant bacteria but almost all studies in Viet Nam showed that multidrug-resistant bacteria in nosocomial pneumonia is high, especially in the ICU department. Also, resistance genes analysis of bacteria and history of using any kind of antibiotics haven't been done in this research. Therefore, further research should be undertaken to cover all agents in NP and determine whether antibiotic cycling can reduce antibiotic resistance, and analyze the resistance genes of bacteria.

5. CONCLUSION

These results show that the resistance of bacteria to quinolones, carbapenem, and cephalosporin is very high, above 80% in the ICU. Moreover, almost all pathogens have had multi-resistance to these antibiotics. In addition, increasing the use of antibiotics can lead to resistant antibiotics, and bacteria, changed antibiotics have been significantly associated with the multi-resistance of bacteria.

Conflict of interest

There is no conflict of interest.

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None to declare.

Ethics approval
The Institutional Review Board approved this observational study of Can Tho University of Medicine and Pharmacy, Vietnam with 1530/QD-DHYDCT in June 2015.

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