



# Increasing Trend of Imipenem-Resistance Among *Acinetobacter baumannii* Isolated From Hospital Acquired Pneumonia in Northeast of Iran

Azad Khaledi,<sup>1</sup> Omid Elahifar,<sup>1</sup> Hossein Vazini,<sup>2</sup> Mohammad Yousef Alikhani,<sup>3</sup> Afsane Bahrami,<sup>4</sup>

Davoud Esmaeili,<sup>5</sup> and Kiarash Ghazvini<sup>1\*</sup>

<sup>1</sup>Antimicrobial Resistance Research Center, Avicenna Research Institute, Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran

<sup>2</sup>Nursing Department Basic Sciences Faculty, Hamedan Branch, Islamic Azad University, Hamedan, IR Iran

<sup>3</sup>Department of Microbiology, Faculty of Medicine, Hamadan University of Medical Sciences, Hamadan, IR Iran

<sup>4</sup>Department of Modern Sciences and Technologies, School of Medicine, Mashhad University of Medical Sciences, Mashhad, IR Iran

<sup>5</sup>Applied Microbiology Research Center, and Microbiology Department, Baqiyatallah University of Medical Sciences, Tehran, IR Iran

\*Corresponding author: Kiarash Ghazvini, MD., PhD, Ghaem Hospital, Ahmad Abad Avenue, Mashhad 91735, IR Iran. Tel: +98-9151248938, Fax: +98-5138409612, E-mail: Ghazvinik@mums.ac.ir

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## Abstract

**Background:** Nosocomial infections due to high mortality and economic cost are one of the most important challenges that hospitals face with it. Reports show that hospital acquired pneumonia (HAP) is the second most common nosocomial infection in some countries such as the United States.

**Objectives:** The aim was to study the frequency and resistance pattern of *Acinetobacter baumannii* isolates against imipenem.

**Methods:** This cross-sectional study was conducted for 2 years on patients with nosocomial pneumonia caused by *A. baumannii* in 2 major university hospitals in Mashhad, Iran. After detection and identification, data regarding mortality, length of hospital stay, and treatment were collected. Furthermore, the pattern of antibiotic resistance was investigated in *A. baumannii* against imipenem.

**Results:** In this study, among 700 patients with nosocomial pneumonia, 364 and 336 of those were male and female, respectively. All of these received imipenem. Of the total patients, 317 cases (45%) were resistant to imipenem. 84% of these patients were cured and the remaining 16% expired (P value = 0.001). *A. baumannii* resistance to the imipenem in both hospitals had an increasing rate. The resistance rate in the Ghaem hospital increased 96.6% at the end of the period compared to beginning of study (P value = 0.004). Also, a similar increase (94.7%) was observed in the Imam Reza hospital (P value = 0.003).

**Conclusions:** According to our results, excessive use of imipenem has been caused by antibiotic resistance, for this, the appropriate selective choice of antibiotics should be considered. At first, other antibiotics such as new generations of cephalosporins should be chosen for empirical treatment of *A. baumannii*.

**Keywords:** Imipenem, Hospital Acquired Pneumonia, *Acinetobacter baumannii*

## 1. Background

Nosocomial infection is one of the most important causes of mortality and complications in hospitals (1). The nosocomial infection is the infection that happens between 48 to 72 hours after admission of patients in the hospital, shortly after hospital discharge, and on admission moment the patient did not have such an infection (2). The people with immunodeficiency or with other underlying diseases (e.g., malignancy, burns or immunosuppression), individuals under treatment with immune suppresser drugs, or people with surgical operations are sus-

ceptible to nosocomial infections (3). Hospital acquired pneumonia (HAP) is a type of pneumonia that occurs 48 hours or later after hospital admittance and is not present at the time of patient admission (4). Reports show that HAP is the second most common nosocomial infection in some countries such as the United States and is accompanied with the highest death and illness. HAP rate is between 5 and 15 cases per 1,000 hospital admissions and is included near 15% of total hospital-acquired infections (5). HAP is responsible for 26% of nosocomial infections in the intensive care unit (ICU) (6). Intubation and mechanical ventilation (MV) are 2 major factors that were involved in HAP (7). ICU

is one of the hospital wards that is critical in the treatment of many severe diseases that require particular cares. Even though this ward is having a noticeable role in the care of patients with infections, ICUs cause some complications, death, and costs imposed on patients. The prevalence of nosocomial infections related to mechanical ventilation is more than that in other hospital wards (8). In recent years, *Acinetobacter baumannii* has emerged as a pathogen can cause serious infection with high mortality and morbidity in different wards of the hospital, especially the ICU, patients encountered with broad-spectrum antibiotics, immunocompromised patients. World health organization (WHO) declared that Multidrug resistance (MDR) strains of *Acinetobacter baumannii* are a significant threat worldwide. In total, many studies have shown that the prevalence of MDR strains of *A. baumannii* has reached an alarming status all over the world (9), including Iran (10, 11). Developing countries such as Iran have serious problems in treating the infections resulted from MDR strains. Long hospitalization periods, prolonged stay in the ICU, exposure to antimicrobial agents, mechanical ventilation, colonization pressure, invasive procedure, recent surgery, and underlying diseases are among the risk factors involved in infection and colonization of MDR strains (12). One study from Turkey revealed that the hospital section spent over 48 million dollars in 1995 for medical management of nosocomial infection (13). The patients mortality rate, with *A. baumannii* infections, in hospitals and in the ICU has reported to range between 7.8% to 23% and from 10% to 43%, respectively (14). The imipenem resistance rate of *A. baumannii* from throughout the world in 2005 to 2009 reached resistance rates of more than 50% (15). The reports from Brooklyn, New York presented that almost 2 out of every 3 isolates were resistant to carbapenem antibiotics (16). In developing countries such as Iran, the incidence rate of carbapenem resistant *A. baumannii* (CNSAb) infections is a rising problem in hospitalized patients (17).

## 2. Objectives

The aim of this study was to evaluate the change of imipenem-resistance pattern against *A. baumannii* in the Ghaem and Emam Reza hospitals.

## 3. Methods

### 3.1. Collecting of Patients Information

In this study, with non-probability sampling, the data of 700 patients who were detected with nosocomial pneumonia caused by *A. baumannii* in Ghaem and Emam Reza hospitals during 2011 to 2013 was collected and the resistance pattern of isolated *A. baumannii* was investigated.

### 3.2. Inclusion and Exclusion Criteria

Patients with Hospital-acquired infection (HAI) during 2011 - 2013 in the Imam Reza and Ghaem hospitals and were treated by imipenem antibiotic, had their information, and results of treatment their records which were also included in present study. Additionally, those who had passed the course of treatment but completed information of their therapeutic was not available were excluded.

### 3.3. Analysis Data Method

After collecting the patient's information, they were placed in a 3 month period in each hospital. First, the mortality rate was calculated for the period of 1 year and the changes in these variables were accounted. The variance rate of the treatment time in the 1 year period was calculated and the rate of change accounted. Since these 2 were independent of each other, a significant percentage was obtained by multiplying them together and by putting it in the table, *Acinetobacter* resistance to the imipenem was reported. Finally, the results were analyzed by the SPSS (chi-Square test) software.

## 4. Results

In this study, among 700 patients with nosocomial pneumonia, 364 were male and 336 people female, respectively. All of these patients received imipenem. Of these 700 patients, 317 cases (45%) were resistant to imipenem. 84% of these patients were cured and the remaining 16% were expired in spite of receiving imipenem. *A. baumannii* resistance to the imipenem antibiotic in both hospitals had an increasing rate. The patients were categorized in 3 groups [(Children (group 1), youth and older adults (group 2) and elderly (group 3)]. Based on this grouping, most of the patients were in the children group. The normal duration of treatment was determined between 1 to 2 weeks; therefore, according to the duration of treatment, 3 groups were formed [treatment for less than appropriate duration (group 1)], [treatment for appropriate duration (group 2)], and [treatment for more than appropriate duration (group 3)]. According to the duration of treatment, 17%, 61%, and 22%, of patients were in group 1, group 2, and group 3, respectively (P value = 0.001). In the period of 2011 - 2012, in the Ghaem hospital, 16% of the studied patients were expired, 48% were in an appropriate duration (group 2), and 36% were in group 3 (in total, between 2 hospitals). Also, in the period of 2012 - 2013 in the Ghaem hospital, 24% of patients were expired and 64% recovered in the appropriate duration of treatment. Totally, in the same condition, an 8% increase in mortality was seen at the Ghaem hospital. Therefore, an average expire was 21 and 25 days during 2011 - 2012 and 2012 - 2013, respectively. However, in

the Emam Reza hospital in 2011 - 2012, 16% of patients were expired and 56% and 28% of them recovered in appropriate duration (group 2, and group 3), respectively (P value = 0.001). In the period of 2012 - 2013 in the Emam Reza hospital, the mortality rate was 8% and 76% cases were recovered in the appropriate duration and 12% recovered in the duration time more than appropriate duration. The highest frequency of patients suffered from infection with *A. baumannii* in 2 hospitals was seen in the ICU ward and the second high frequency was related to the burn ward (Figure 1). As shown in Figure 1, *A. baumannii* resistance to the imipenem antibiotic in Ghaem hospital was 150 cases (43%) and this rate in the Emam Reza hospital was reported 167 (48%). In both hospitals, the imipenem resistance had an increasing rate. The resistance rate in the Ghaem hospital increased 96.6% at the end of the period compared to the beginning of study (P value = 0.004). Also, similar increase (94.7%) in imipenem resistance was observed in the Imam Reza hospital (P value = 0.003) (Figures 1 and 2).

## 5. Discussion

Nosocomial infection is one of the most common troubles in hospitals and is directly associated to raise costs and hospitalization time. Based on the WHO report, the frequency of nosocomial infection in developed countries is less than 5%, but in developing countries this rate varies (18). World health organization (WHO) reported that in 2005 more than 4.4 million nosocomial infections occur annually in the world (5). The most important note is that without full information on nosocomial infections, control and prevention of these infections is nearly difficult. With regard to purposed guidelines by WHO, each hospital should have an active infection control committee (3). The most common factors are involved in nosocomial infection including; incomplete decontamination in wards, utilize of shared devices, and so on (19). Hospital-acquired pneumonia (HAP) or nosocomial pneumonia are results from gram negative bacteria (such as; *Pseudomonades*, *E. coli*) and was reported 55% to 85% and gram positive bacteria accounted for 20% to 30% (7). The common etiological causes of nosocomial infection are gram negative bacilli such as *E. coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *A. baumannii*, and *Staphylococcus* (20). In regards to this point, *A. baumannii* has the most important role in HAP infection. The infectious diseases society of America placed this bacterium as a third organism on a hit list of a 6 top priority hazardous drug resistant bacteria due to its tendency to develop drug resistance and because of the absence of new drugs to treat infections result from resistant *Acinetobacter Baumannii* (21). Several predisposing risk factors for infection with this bacterium include; prolonged length

of hospital stay, immunodeficiency, surgery, burns, aging, anti-bacterial agents, and invasive devices (22). Treatment of infections caused by this bacterium typically involves using beta-lactams and fluoroquinolones. In recent years, the increased use of antibiotics has led to the emergence of resistant strains (23). Antibiotic resistance to *Acinetobacter baumannii* may be acquired and intrinsic mechanisms, which these mechanisms include the enzyme, mutations in the gene target, the permeability of the outer membrane, and increase in expression of the efflux pumps (16, 23). Today infection with multidrug-resistant (MDR), means that strains of *Acinetobacter baumannii* that are resistant to 3 current classes of antibiotics as well as strains of *Acinetobacter baumannii* in addition resistant to 3 common classes of antibiotics are resistant to imipenem as well and, are called extreme drug resistance (XDR) is increasing (24). This has created therapeutic implications and led to difficulties in treatment infections related to this bacterium and led to an increased length of stay, increased health care costs, an unfavorable prognosis and more mortality than sensitive strains (25, 26). Carbapenems are a good choice for the treatment of resistant strains, are the class of beta-lactams that have broad antimicrobial activity, and used as a main choice for the treatment of resistant strains (24, 25). MDR strains of *Acinetobacter baumannii* are resistant to carbapenems, Multidrug-resistant *Acinetobacter baumannii* resistant to carbapenems (MRAB-C) are also on the rise, to treat these, Colistin and Tigecycline is recommended in many references (25). Levels and different patterns of antibiotic susceptibility among different species of *Acinetobacter baumannii* has been achieved and shows that there is a higher prevalence of antibiotic resistance among *Acinetobacter baumannii* species compared with other *Acinetobacter* species (27, 28). Our study showed that the *A. baumannii* is increasing, in line with this, Khashibai et al. reported *A. baumannii* as the high frequent organism with a prevalence rate 40.4% (29). *A. baumannii* is an opportunistic pathogen, which affects different groups of people, especially those admitted to the ICU (22). Furthermore, our results found that the trend *A. baumannii* resistant strains to imipenem was increasing, in confirming this finding, some studies have also reported this phenomenon (9, 30, 31). In a study of 298 positive cultures of *A. baumannii* isolated from American soldiers in the Iraq war who were hospitalized at military hospitals between 2003 and 2008, showed that 46 (15%) were resistant to imipenem (32). Similar to the present study, in several studies, the most nosocomial infection was found in the ICU, the reasons for this is likely due to the sensitivity of the ICU, prescribing the high rate of stronger antibiotics, and use of equipment such as ventilator, suction, intravenous catheters, oxygen, and chips in this ward have an increased risk of infection

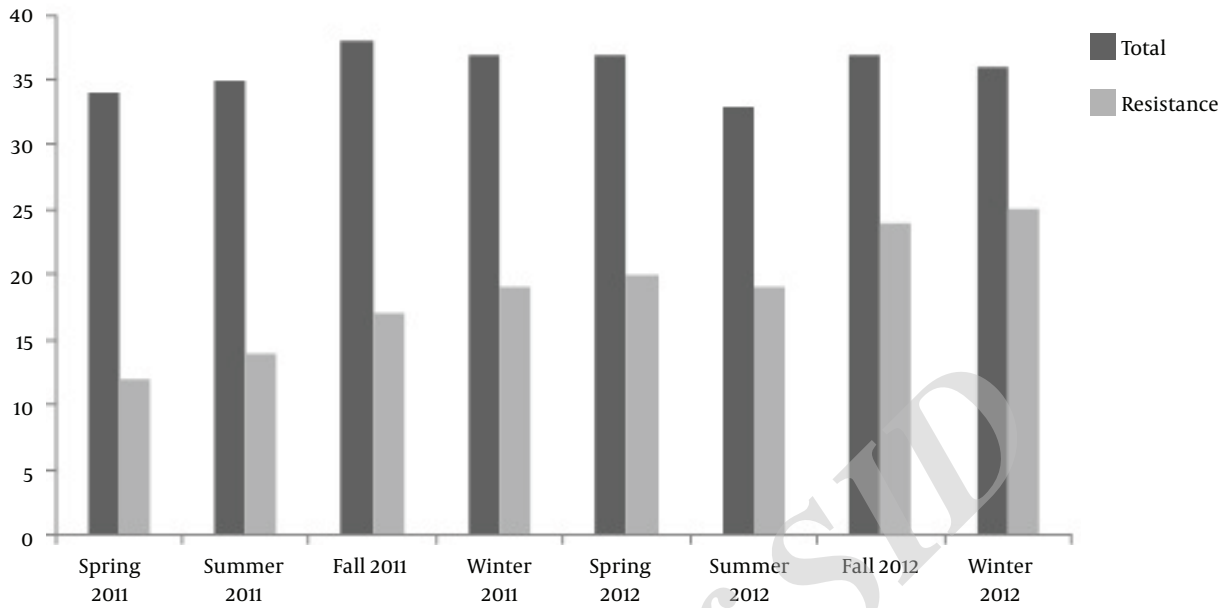


Figure 1. The Frequency of Resistance Rate in *A. baumannii* to Imipenem from Ghaem Hospital

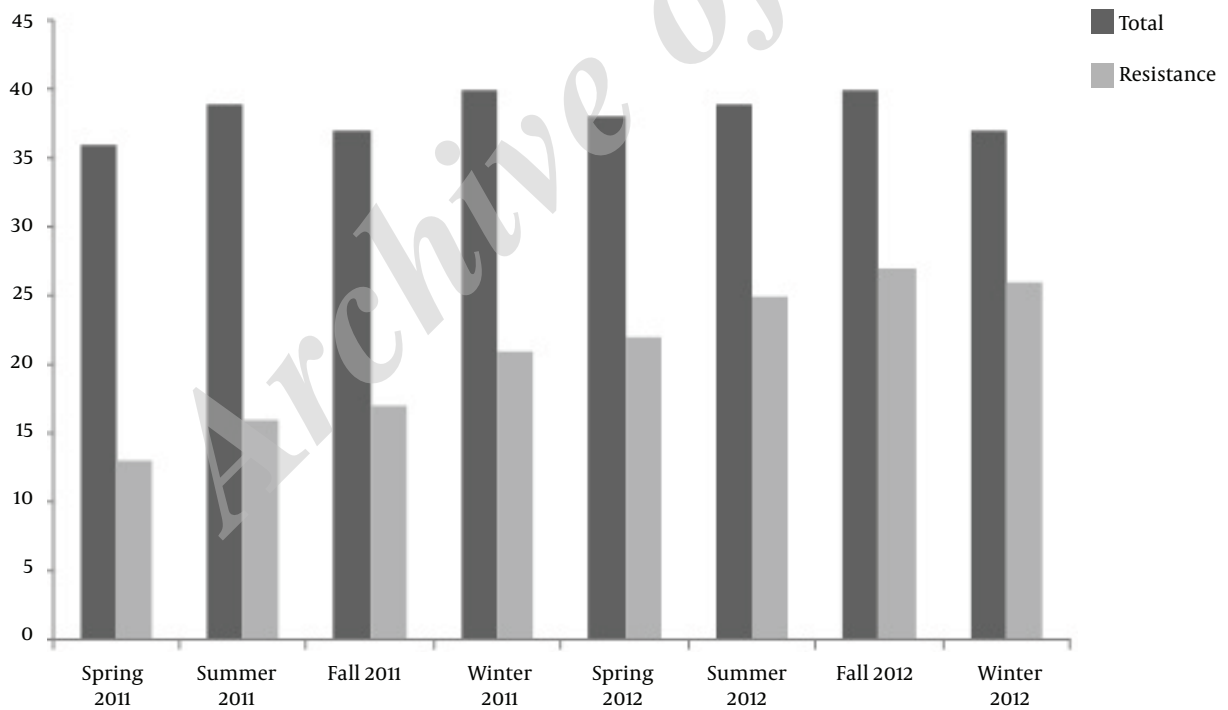


Figure 2. The Frequency of Resistance rate in *A. baumannii* to Imipenem from Emam Reza Hospital

(33). According to the results of the present study, 700 samples from 2 hospitals were collected and none of these were

deleted. All of patients were placed in 3 groups [Treatment lower than normal duration (group 1)], [Treatment in nor-

mal duration (group 2)], and [Treatment more than normal duration (group 3)]. Based on this grouping, as the length of the treatment period increased, bacterial resistance to the analysis showed that the age of patients has a significant relationship with infection with *A. baumannii*. Due to immune insufficiency, the infection with *A. baumannii* is more common in children and older people. In total, the trend of changing pattern of *A. baumannii* resistance to the imipenem antibiotic has increased, which is a sign of drug resistance in the mentioned organism.

### 5.1. Conclusions

According to our results, excessive use of imipenem has been caused by antibiotic resistance, for this, appropriate selective choice of antibiotics should be considered. At first, other antibiotics such as new generations of cephalosporins should be chosen for empirical treatment of *A. baumannii*.

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### Footnotes

**Authors' Contribution:** Study concept and design: Azad Khaledi and Mohammad Yousef Alikhani, drafting of manuscript: Omid Elahifar and Hossein Vazini; critical revision of the manuscript for important intellectual content: Davoud Esmaeili and Kiarash Ghazvini; performance of laboratory tests/statistical tests: Omid Elahifar and Azad Khaledi.

**Conflict of Interest:** None declared

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