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Pattern of antibiotic resistance in nosocomial infections with Gram-negative bacilli in ICU patients (Tehran, Iran) during the years 2012-2014

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ABSTRACT

Background and Objective: Owing to the new patterns of antibiotic resistance, selection of the appropriate antibiotics for the treatment of nosocomial infections, especially gram-negative bacilli, has become a big challenge. Therefore, the aim of this study was to evaluate the antibiotic resistance of nosocomial infections with Gram-negative bacilli in Iran during the years 2012-2014.

Materials and Methods: In this cross-sectional study, samples of the culture of patients with nosocomial infections in various departments of the Shahid Mostafa Khomeini hospital of Tehran were studied over a three-year period. Information on the culture-positive blood, urine, sputum, and exudates in terms of the presence of the most common nosocomial aerobic Gram-negative bacilli (*Acinetobacter baumannii*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*), the type of consumed antibiotics, and an antibiotic susceptibility test was extracted from patient records and recorded in the information forms.

Results: The percentage of *P. aeruginosa* resistance has increased during the study period as compared to the colistin, meropenem, imipenem, gentamicin, and ceftazidime antibiotics. *A. baumannii* and *E. coli* bacteria showed the highest resistance, while the maximum susceptibility was observed in this period to ampicillin and colistin. The high resistance of *K. pneumoniae* was also observed to cefotaxime and ampicillin, but this bacterium had a high susceptibility to colistin and meropenem.

Conclusion: The results obtained from the antibiotic resistance of the studied bacteria during the three years of the study demonstrates the increasing prevalence of the resistance of Gram-negative bacteria to common and available antibiotics. This could become a major clinical crisis in the near future.

1. Introduction

Since 1960s, the term 'nosocomial infection' has been taken to mean an infection that people contract 48-72 hours after hospitalization (1,2). Nosocomial infections occur in two million individuals annually, causing 19,000 deaths (3). It has been found that nosocomial infections are the sixth leading cause of death in the United States and somewhat Europe (4). Additionally, nosocomial infections lead to economic and insurance administrative problems in communities and increases high missionaries to treatment costs with an average of 5–7 days increase in hospitalization (5,6). Although more than a third of nosocomial infections are preventable (7), the estimated costs for the health care budget of United States have been reported to be 5–10 billion dollars, and this budget is 28–42 billion dollars in the world (8,9).

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Infections caused by Gram-negative bacteria have characteristics that contribute to the special concerns. The bacteria have high abilities for regulation and obtaining the genes that encode the mechanisms associated with antibiotic resistance, especially if there is too much consumption of antibiotics. In addition, the bacteria have access to a set of resistance mechanisms and often use multiple resistance mechanisms against antibiotics and sometimes use one mechanism against multiple antibiotics (10). Recent data obtained from the National Grid of America's health care safety demonstrate that Gram-negative bacteria are responsible for over than 30% of nosocomial infections and that the bacteria are dominant in ventilator-associated pneumonia and urinary tract infection (11). In intensive care units in the United States, Gram-negative bacteria are responsible for approximately 70% of infections, and similar data from other parts of the world also mention similar results (10). A range of Gram- negative organisms are responsible for nosocomial infections. The *Enterobacteriaceae* family is the most commonly known group. Unfortunately, multidrug-resistant organisms have been reported such as *P. aeruginosa*, *Acinetobacter*, and *Enterobacter Baumannii* increasingly producing beta-lactamase or carbapenemase throughout the world (12). In hospitals in the United States, a significant percentage of *K. pneumoniae* infection resistance to third-generation cephalosporins and carbapenems, *P. aeruginosa* resistance, and resistance of ventilator-associated *A. baumannii* causing pneumonia to carbapenem have been observed (11). Additionally, higher levels of resistance have been reported in parts of Europe (13). One of the biggest concerns in this regard is that infections caused by organisms are resistant to all commonly available antibiotics such as polymyxin (14,15).

Delays in the administration of appropriate antibiotics can cause increased mortality among patients with bloodstream infections acquired in hospital (16). The main challenge lies in the selection of the appropriate antibiotic for treatment that has been obtained based on the information from its antimicrobial resistance pattern in the region. Acquisition of antibiotic resistance genes by bacteria over time and in different geographical areas, as well as changes in the susceptibility of bacteria to antibiotics, shows the need for more research in this field among different populations (17,18). On the other hand, in most studies, antibiotic resistance is generally expressed in the results. Therefore the aim of this study was to evaluate the antibiotic-resistance pattern of nosocomial infections with Gram-negative bacilli in Iran during the years 2012–2014, which has been provided separately in a table. Thus, the antibiotic resistance of different bacteria to any of the conventional antibiotics was evaluated during these three years and would lead to the better and easier conclusion.

2. Materials and Methods

In this cross-sectional study, samples of blood culture of patients with nosocomial infections at Shahid Mostafa Khomeini hospital in Tehran were examined on a three-year period from 2012 to 2014. Inclusion criteria was positive culture samples among patients hospitalized more than 48 hours and then they caught fever. While samples of patients who were in the other infection clinical incubation period based on the clinical symptoms and were younger than 12 years old, were excluded from the study. Information related to the positive results of blood, urine, sputum, and exudate cultures were excluded due to the presence of the most common nosocomial aerobic Gram-negative bacilli "*A. baumannii, E. coli, P. aeruginosa*, and *K. pneumonia"* (19). The types of antibiotics and antibiogram were obtained from the patient records and information was recorded in the forms. Collected data were analyzed by SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) application.

3. Results

In this cross-sectional study, 610 cases have been analysed to assess the antibiotic resistance of nosocomial infection. In terms of antibiotic resistance during the studied years, a total of 32 antibiotics were used for testing antibiogram, which we examined abundantly for ease of use (Table 1).

Table 1. Frequency of bacteria isolated from patients' cultures separated by antibiogram

Antibiogram	Sensitive		Resistant	
Antibiotic	Frequency	Percentage	Frequency	Percentage
Colistin	304	49.8	4	0.7
Amikacin	132	21.6	341	55.9
Gentamicin	211	34.6	327	53.6
Cefotaxime	24	3.9	391	64.1
Ceftazidime	53	8.7	358	58.7
Meropenem	203	33.3	181	29.7
Imipenem	280	45.9	104	17
Ciprofloxacin	134	22	401	65.7
Cotrimoxazole	138	22.5	235	38.5
Cefepime	50	8.2	169	27.8
Ampicillin	18	3	380	62.2
Vancomycin	113	18.5	10	1.6
Tetracycline	60	9.8	61	10
Nitrofurantoin	94	15.4	61	10
Nitrofurantoin	21	3.4	70	11.4

A. baumannii showed the highest resistance to ampicillin in the years 2012-2014. *A. baumannii* bacteria were the most susceptible to Colistin in the years 2012-2014. After Colistin, the highest sensitivity was observed in 2012 to meropenem with 73.3%, and in 2013 and 2014 to imipenem with 69% and 43.8% (Table 2).

Table 2. Antibiotic resistance of *Acinetobacter baumannii* isolated from patients from 2012 to 2014

Year	2012		2013		2014	
Antibiotic Resistance	Sensitive percentage	Resistance percentage	Sensitive percentage	Resistance percentage	Sensitive percentage	Resistance percentage
Colistin	100	0	100	0	100	0
Meropenem	73.3	26.7	55.2	44.8	34	66
Imipenem	71.1	28.9	69	31	43.8	56.2
Amikacin	24.4	75.6	25.9	74.1	4.2	95.8
Gentamicin	20	80	27.6	72.4	6.7	93.3
Cefepime	0	100	7.1	92.9	9.5	90.5
Ceftazidime	4.5	95.5	6.9	93.1	2.3	97.7
Cefotaxime	6.8	93.2	7	93	2.5	97.5
Ciprofloxacin	9.1	90.9	7.1	92.9	4.3	95.7
Cotrimoxazole	10	90	9.5	90.5	9.1	90.9
Ampicillin	0	100	0	100	0	100

E. coli in 2012 had a sensitivity of 100% to colistin, imipenem, and nalidixic acid. In 2013, colistin and nalidixic acid retained sensitivity, but in 2014, only colistin was effective on 100% of *E. coli*. *E. coli* in 2012 were the most resistant to ampicillin and cefotaxime with 82.4%. In 2013 and 2014, the highest resistance was observed to ampicillin with 93.6% and 96.6%, while cefotaxime and ceftazidime were in the next ranks (Table 3).

Table 3. Antibiotic resistance in *Escherichia coli* isolated from patients from 2012 to 2014

Year	2012		2013		2014	
Antibiotic Resistance	Sensitivity percentage	Resistance percentage	Sensitivity percentage	Resistance percentage	Sensitivity percentage	Resistance percentage
Colistin	100	0	100	0	100	0
Meropenem	87.5	12.5	77.8	22.2	78.9	21.1
Imipenem	100	0	78.3	21.7	80	20
Amikacin	47.1	52.9	36.2	63.8	32.2	67.8
Gentamicin	64.7	35.3	55.3	44.7	30.5	69.5
Ceftazidime	18.8	81.2	12.8	87.2	18.5	81.5
Cefotaxime	17.6	82.4	9.5	90.5	13	87
Ciprofloxacin	70.6	29.4	51.1	48.9	54.2	45.8
Cotrimoxazole	52.9	47.1	53.2	46.8	49.2	50.8
Nitrofurantoine	71.2	28.8	55.3	44.7	56.2	43.8
Nalidixic Acid	100	0	100	0	44.7	55.3
Ampicillin	17.6	82.4	6.4	93.6	3.4	96.6

In 2012, *P. aeruginosa* had a sensitivity of 100% to colistin, meropenem, and imipenem. In 2013, a sensitivity of 100% was observed to colistin. In 2014, *P. aeruginosa* was found to be resistant to colistin, which was sensitive only to streptomycin. In 2012, all samples of *P. aeruginosa* were resistant to cefepime, cefotaxime, and amikacin. In 2013, 100% resistance was to the antibiotics of cefotaxime, trimethoprim-sulfamethoxazole, and ampicillin. In 2014, all the samples of *P. aeruginosa* were resistant to ampicillin and trimethoprim-sulfamethoxazole (Table 4).

Table 4. Antibiotic resistance in *Pseudomonas aeruginosa* isolated from patients from 2012 to 2014

Year	2012		2013		2014	
Antibiotic Resistance	Sensitivity percentage	Resistance percentage	Sensitivity percentage	Resistance percentage	Sensitivity percentage	Resistance percentage
Colistin	100	0	100	0	94.7	5.3
Meropenem	100	0	70.9	29.1	59.9	40.1
Imipenem	100	0	73.9	26.1	72.2	27.8
Amikacin	0	100	8.7	91.3	8.7	91.3
Gentamicin	60	40	34.8	65.2	44.4	55.6
Cefepim	0	100	8.7	91.3	11.8	88.2
Ceftazidime	60	40	43.5	56.5	35.5	46.7
Cefotaxime	0	100	0	100	11.8	88.2
Ciprofloxacin	20	80	21.7	87.3	25.5	74.5
Cotrimoxazole	-	-	0	100	0	100
Ampicillin	-	-	0	100	0	100

K. pneumoniae had the highest sensitivity to colistin during the years 2012–2014. *K. pneumoniae* revealed the highest resistance to ampicillin and cefotaxime in 2012 each with 92.3%. In 2013 also these two drugs showed 100% resistance. There was also 100% resistance to ampicillin in 2014 (Table 5).

Table 5. Antibiotic resistance in *Klebsiella pneumoniae* isolated from patients 2012 to 2014

Year	2012		2013		2014	
Antibiotic Resistance	Sensitivity percentage	Resistance percentage	Sensitivity percentage	Resistance percentage	Sensitivity percentage	Resistance percentage
Colistin	100	0	100	0	100	0
Meropenem	69.2	30.8	53.8	46.2	40	60
Imipenem	92.3	7.7	96.2	3.8	66.7	33.3
Amikacin	23.1	76.9	23.1	76.9	26.8	73.2
Gentamicin	61.5	38.5	61.5	38.5	39	61
Cefepim	15.4	84.6	8	92	2.6	97.4
Ceftazidime	15.4	84.6	15.4	84.6	2.6	97.4
Cefotaxime	7.7	92.3	0	100	2.6	97.4
Ciprofloxacin	23.1	76.9	23.1	76.9	7.3	92.7
Ampicillin	7.7	92.3	0	100	0	100

4. Discussion

Based on the results of our study, bacteria leading to nosocomial infections had the highest resistance to colistin with 49.8% and imipenem with 45.9%. In Mohammadi Mehr et al studies, imipenem was identified as the most effective antibiotic against Gram-negative bacteria (20,21). However, in these studies, the sensitivity of bacteria to colistin was not examined. In studies conducted in China (22), Brazil (23), and United States (24), along with the study by Haddadi (25), imipenem was reported as the most effective antibiotic against the Gram-negative strains. Results of our study demonstrated that all samples of *A. baumannii* over three years were sensitive to Colistin, but the sensitivity to meropenem decreased from 73.3% in 2012 to 34% in 2014, and also sensitivity to imipenem decreased from 71.1% in 2012 to 43.8% in 2014. Additionally, the sensitivity of *Acinetobacter spp.* cases to amikacin and gentamicin antibiotics

significantly decreased during the study years. In the last year of study with the 11 tested antibiotics, more than 90% resistance was observed to 8 antibiotics. All samples of *Acinetobacter spp.* were resistant to ampicillin during the study. In a study by Amini et al in which the frequency of nosocomial infection caused by *A. baumannii* has been examined in patients hospitalized in in intensive care unit of Mostafa Khomeini hospital from 2008 to 2011, *Acinetobacter* samples revealed the highest sensitivity to amikacin with 14.6% and 97.7% of the studied subjects were resistant to imipenem (26), however, in this study like the present study, all *Acinetobacter* samples were resistant to several categories of drugs, while in the study of Hujer at least 89% of isolates were resistant to more than three classes of antibiotics (27). In Mohammadi Mehr and colleagues study, *Acintobacter spp.* showed higher resistance than the other Gram-negative organisms and had complete resistance to 9 antibiotics (21). Additionally, in a study conducted in Chicago, *Acinetobacter spp.* was resistant to all available common antibiotics and was associated with high mortality (28). Similar results were achieved in Spain in 2004 (29). In Faizabadi and colleagues study, *A. baumannii* was found to be resistant to ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, and ampicillin above 83–100% (30). Mohammadi Mehr et al study showed that *A. baumannii* isolates showed 60–100% resistance to 13 from 15 antibiotic disks (20). The results of these studies indicated very high resistance of *A. baumannii* to almost all commonly available antibiotics. The cause of this high resistance can be the increasing tendency to use antibiotics to treat viral infections, incorrect detection of diseases, inappropriate duration and dose of treatment, and arbitrary use of antibiotics by people in general. Due to the increasing incidence of infection with the *A. baumannii* bacteria, this issue can become an important clinical crisis in the near future. In the present study, *E. coli* bacterium as the other common bacterium had 100% sensitivity to Colitin antibiotics in all years of study, and then the greatest sensitivity was observed to the antibiotics imipenem and meropenem. *E. coli* revealed highest resistance to ampicillin, cefotaxime, and ceftazidime. In Mohammadi Mehr and collagenous studies, *E. coli* had the highest sensitivity to imipenem, and then Nitrofurantoine and the greatest resistance was reported to ampicillin (20,21), which are similar to our results. Fallah and colleagues found that *E. coli* had highest resistance to amoxicillin, cotrimoxazole, cefazolin and Cefixime, and highest sensitivity to amikacin and nitrofurantoine (31). As can be seen, the highest resistance was found to beta-lactams. Since beta-lactams are the most popular antibiotics in the world, creation of resistance to them has gained in importance in the last two decades. In Iran, too, cephalosporins are most commonly used due to the availability and safety that is associated with an increased risk of resistance. According to the results of this study, *P. aeruginosa* isolates, except in one case, were sensitive to the colistin antibiotic. The greatest sensitivity was observed to imipenem and meropenem. Of course, resistance to imipenem and meropenem dramatically increased during the study year, which is indicative of an excessive consumption of antibiotics during the study years that destroyed 100% sensitivity to antibiotics in the first year. *P. aeruginosa* isolates demonstrated 100% resistance to antibiotics of ampicillin and co-trimoxazole, and then the highest resistance was observed to amikacin. Results of Mohammadi Mehr et al study showed that *P. aeruginosa* isolates had the highest sensitivity to imipenem and had 100% resistance to antibiotics such as ampicillin, cotrimoxazole, and nitrofurantoine (20), which is almost identical to our results. Mohammadi Mehr and collageous also found that *P. aeruginosa* strains was the most sensitive to imipenem, ciprofloxacin, and amikacin, while the highest resistance was observed to Nitrofurantoine, ampicillin, and then co-trimoxazole (21). Madani et al also found that in Morocco the resistance of *P. aeruginosa* isolates to ceftazidime is 35.6% (32), which is lower than our study, and this can be caused by excessive consumption of cephalosporins in our country. Based on the results of our study on *K. pneumoniae* bacteria, all isolates of the bacteria were susceptible to Colistin and then the highest sensitivity was observed to imipenem. *K. pneumoniae* isolates demonstrated the highest resistance to Ampicillin and then to cefotaxime and ceftazidime. The highest sensitivity was observed to imipenem and amikacin, which was somewhat similar to our study (20). Results of Faizabadi et al study demonstrated that all *Klebsiella* isolates were susceptible to imipenem and meropenem and also resistance to ciprofloxacin and gentamicin only in 37% and

33% of cases (30), which is much less in our study. The reason for this difference could be the difference in the time and place of the above study which is effective on antibiotic resistance. The results of the examination of antibiotic resistance of bacteria in three years demonstrate increasing prevalence of Gram-negative bacteria resistance to common and available types of antibiotic that except colistin antibiotics that is not very common used, has considerable resistance compared to other antibiotics that is increasing every year and can become clinically an important crisis in the near future.

In order to prevent the creation of resistant strains, administration of the drug without necessity should be avoided. If antibiotics are prescribed in the requirements, effective antibiotics should be selected according to the antibiogram. It is also recommended that periodic monitoring of ulcer, sputum, and urine cultures should be carried out in the hospital environment to identify susceptibility faster. Hospital infection control committees should select special provisions in the field of microbial control. The most important actions are training nurses who have the most frequent interactions with patients during the course of treatment. In addition to shorter and more certain indication usage of urinary catheters, vascular and tracheal tube, the establishment of a broad education system for nurses, specialists, students, and all health care staff will be effective for nosocomial infections. Since antimicrobial resistance among bacteria causing nosocomial infections is increasing annually, it seems that the implementation of research in order to detect these infections and antibiotic resistance on the one hand and the identification of risk factors for these infections on the other hand are essential.

The results obtained from the antibiotic resistance of the studied bacteria during the three years of this study demonstrates the increasing prevalence of the resistance of Gram-negative bacteria to common and available antibiotics. This could become a major clinical crisis in the near future.

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