Risk Factors Associated With Imipenem-Resistance Among Isolated Gram-Negative Bacteria From Patients in Sanandaj Hospitals, Iran

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Abstract

Background: The use of imipenem antibiotics against Gram-negative bacteria is growing, but the incidence of imipenem-resistant bacteria is also increasing.

Objectives: The aim of this study was to determine the risk factors for imipenem resistance in patients with Gram-negative bacteria infections.

Patients and Methods: An imipenem minimum inhibitory concentrations (MIC) test was done using the E-test, and a survey of different risk factors of imipenem resistance in 374 patients who were infected solely by Gram-negative bacteria was performed.

Results: Of the 374 isolated, 134 were imipenem resistant, and 240 were sensitive to imipenem. The resistance rate was more common in males and in patients with intensive care unit (ICU) admission, trauma-induced infections, a history of antibiotic use, the need for ventilator support, or central venous catheter insertion, and in nosocomial infections.

Conclusions: Our results showed the rate of effects of different risk factors on imipenem resistance. Regarding the studied risk factors, appropriate programs must be set in place to control and prevent imipenem resistance in Gram-negative bacteria.

Keywords: Risk Factors, Imipenem, Gram- Negative Bacteria, Drug Resistance

1. Background

The antimicrobial resistance of bacteria leads to problems in controlling and treating infections (1). Drug resistance can result in treatment failure, increased morbidity and mortality (especially in critically ill patients), prolonged hospitalization, and higher healthcare costs (2). The risk factors for imipenem resistance in patients have been determined in many studies (1), and different studies have shown the resistance to imipenem in various bacteria. Zilberberg et al. (3) In the US, used a systematic literature review to show that imipenem-resistant bacteria was present in 14.6% of the isolates of patients with pneumonia. In another study, Sorin et al. (4). Also in the US, demonstrated that the nosocomial transmission of imipenem-resistant *Pseudomonas aeruginosa* is related to bronchoscopy, which is associated with improper connection to the steris systems. Also, Huang et al. (2) In Taiwan, reported that, in 329 patients with *Acinetobacter nosocomialis* bacteremia, 20.4% showed no susceptibility to imipenem.

2. Objectives

We conducted this study to identify the risk factors related to imipenem resistance in Gram-negative bacteria isolated from patients of Sanandaj hospitals, in Iran.

3. Patients and Methods

3.1. Study Population and Specimen Types

We conducted a descriptive, analytic, cross-sectional study on clinical isolates, obtained from patients of Sanandaj Hospitals, located in the Kurdistan province of Iran (from January 2007 through January 2010). Isolates were collected from clinical samples, including the bloodstream, the respiratory tract, skin and soft tissues, and urinary tract infections. On the basis of this study, patients that had at least one imipenem-resistant isolate were considered as cases, and patients who were infected by sensitive isolates during the duration of this study were defined members of the control group, when considering a particular condition related to risk factors during study time.

3.2. Microbiological Methods

All clinical samples were routinely cultured on MacConkey and blood agar (Merck, Germany) plates. Blood samples were cultured in Castaneda blood culture bottles. Isolates were identified at the species level using standard biochemical tests and microbiological methods. Only one isolate per patient was included in this study.

3.3. Antibiotic Susceptibility Testing

Imipenem minimum inhibitory concentration (MIC) tests were done using E-test strips (AB Biodisk, Swede) according to National Committee for Clinical Laboratory Standards (NCCLS); Imipenem-sensitive $\leq$ 4 mg/lit, imipenem-resistant $\geq$ 16 mg/lit (5).

3.4. Risk Factor Detection

For each patient, the following clinical data were collected prospectively in a checklist of different parts, including demographic data, diagnosis at admission, type of clinical ward, current remedy for the patient, history of using antimicrobial agents, isolation site of the bacteria, the presence of mono or poly microbial infections, clinical outcome, and underling diseases. The sources of all clinical specimens were noted in this study, and the results of laboratory tests were compared and matched with the checklists.

3.5. Statistical Analysis

We compared the characteristics of this study using a univariate analysis, and variables were entered in a logistic regression analysis. The chi-square or Fisher's exact test was used for the comparison of dichotomous variables. The odds ratio (OR) and 95% confidence intervals (95% CI) were calculated. Statistical analyses were performed using the software program SPSS 16 for Windows (P values $\leq$ 0.05) (SPSS Inc., Chicago, IL, USA).

4. Results

In this study, 374 Gram-negative bacterium isolates were considered for evaluation. Therefore, 134 (35.8%) patients were considered as the case and 240 (64.1%) patients were considered the control. The majority of isolates were taken from female patients: 231 (61.7%). Results showed that imipenem sensitivity in females (67.09%) was more prevalent than in the males (55.24%). Intensive care unit (ICU) admission, trauma-induced infections, a history of antibiotic use, the need to ventilator support or for the insertion of central venous catheter, and nosocomial infections significantly increased the risk of imipenem resistance in Gram-negative bacteria. Univariate analyses of potential risk factors for imipenem-resistant isolates indicated cefepim use (68.42%) as the potential risk factor for the resistance of Gram-negative bacteria to imipenem, with a CI of 95% (0.09 - 0.69) and P = 0.00 (Table 1).

Table 1. The Frequency of Risk Factors and Imipenem Sensitivity[a]

Risk Factors	Imipenem- Sensitive[b]	Imipenem Resistant[b]	Total	P Value	OR Lower	OR Upper
Gender						
Male	79 (55.24)	64 (44.75)	143			
Female	155 (67.09)	76 (32.90)	231	.02	.39	0.92
Underlying disease						
Yes	23 (54.76)	19 (45.23)	42			
No	211 (63.55)	121 (36.64)	332	.31	.36	1.32
Previous treatment *with antibiotics*						
Yes	14 (50)	14 (50)	28			
No	220 (63.58)	126 (36.41)	346	.16	.26	1.24
ICU stay						
Yes	28 (43.75)	36 (56.25)	64			
No	205 (66.34)	104 (33.65)	309	.00	.22	0.68
Ventilator support						
Yes	24 (37.50)	40 (62.50)	64			
No	209 (67.63)	100 (32.36)	309	.00	.16	0.50
Trauma-induced infections						
Yes	18 (39.13)	28 (60.86)	46			
No	216 (65.85)	112 (34.14)	328	.00	.17	0.62
Need for central venous catheter						
Yes	9 (32.14)	19 (67.85)	28			
No	225 (65.02)	121 (34.97)	346	.00	.11	0.58
Blood transfusion						
Yes	31 (44.28)	39 (55.71)	70			
No	203 (66.77)	101 (33.22)	304	.00	.23	0.67
Nosocomial infection						
Yes	23 (38.98)	36 (61.01)	59			
No	211 (66.98)	104 (33.01)	315	.00	.17	0.55
Antibiotic use in the past 14 days						
Yes	12 (41.37)	17 (58.62)	29			
No	222 (64.34)	123 (35.65)	345	.01	.18	0.84
Cefepim use						
Yes	6 (31.57)	13 (68.42)	19			
No	228 (64.22)	127 (35.77)	355	.00	.09	0.69

[a]OR: 95% confidence interval, these p-values stand and OR for comparison between males and females, and Yes and No.
[b]Data are presented as No. (%).

5. Discussion

This is the first study on risk factors related to imipenem resistance in Gram-negative bacteria in Sanandaj Hospitals, Iran. In our study, the results of the statistical tests performed on 374 patients over four years showed that there are significant statistical differences between the studied risk factors and imipenem resistance (P values < 0.05). In Zavascki's study, there was not a significant statistical correlation (P value ≥ 0.05) between gender and imipenem resistance in *P. aeruginosa*, which is not similar to our study, but there was a significant statistical correlation between mechanical ventilation and imipenem resistance (P value ≤ 0.05) (6). Different Gram-negative bacteria could serve as a reservoir of beta lactamase genes, so it is possible that those mobile genetic elements, such as plasmids that carry antibiotic-resistant genes, spread among bacteria, from strain to strain, and in different species of Gram-negative bacilli (7). The reasons for antibiotic resistance, especially β-lactam antibiotics, vary, but drug inactivation (by β-lactamases), insensitivity of the target (altered penicillin-binding proteins), decreased permeability (altered Gram-negative outer-membrane porins), and active efflux are some of them. Also, bacteria strains that produce Extended-Spectrum β- Lactamases (ESBLs) are capable of degrading the expanded-spectrum cephalosporins and monobactams, and show multidrug resistance to more than one antibiotic (8). Our study's identification of an ICU stay as a strong risk factor for imipenem-resistance was not unexpected [OR = 8.32, CI95% (4.94 – 14.01)], since it had been identified as such in Onguru's and Lee's (P value ≤ 0.005) studies as well (1, 9). In general, it can be concluded that the causes of emergence and the spread of antibiotic-resistant bacteria in healthcare facilities (HCFs) are multifactorial. Some of these factors are: widespread use of antibiotics, cross-transmission from patient to patient, inappropriate or poor infection control measures, inter-hospital transfer of resistance, the acquisition of organisms from the hospital environment, a community contribution of resistance, and so on (10). A limitation of this study is that we were unable to assess the role of patient-to-patient transmission, so this can be considered a bias among our results. In conclusion, this study showed different risk factors for imipenem resistance. However, our results suggest that the risk factors for imipenem resistance are strongly related to ICU stay in patients. Extensive use of other broad-spectrum antibiotics also increases the risk of imipenem resistance, so appropriate programs must be set in place to control and prevent such resistance in patients with these risk factors. There is hope that more studies will be done on the mentioned risk factors and the "how" of gaining antibiotic resistance in bacteria.

Acknowledgments

Footnotes

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