Erciyes Med J 2019; 41(3): 312–5 • DOI: 10.14744/etd.2019.43179
ORIGINAL ARTICLE – OPEN ACCESS



# Economic Burden of Multidrug-Resistant Gram-Negative Infections in a Developing Country

Ayşegül Ulu Kılıç[1], Gamze Kalın Ünüvar[1], Fatma Cevahir[2], Emine Alp[3]

ABSTRACT

**Objective:** Antibiotic-resistant infections represent a significant global public health threat due to their rising prevalence. The aim of this study is to identify risk factors for acquisition of multidrug-resistant gram negatives (MDR-GNs) in the first intensive care unit (ICU) infection episode of patients and also to calculate the economic burden of infection with MDR-GNs that the ICU patient faced.

**Materials and Methods:** This is a prospective observational study conducted over 1 year. The first ICU infection episode of the patients was included into this study. A case was defined as a patient who had an MDR-GN in his or her first episode of an ICU infection, and control was defined as a patient who had a non-MDR-GN in his or her first episode of an ICU infection.

**Results:** A total of 100 patients were included into the study. Sixty-two patients had the MDR-GN, and 38 patients had a non-MDR pathogen. Independent risk factors associated with the MDR-GN infection were the APACHE II score (OR=1.08, p=0.012), transfer from another hospital (OR=9.3, p=0.04), antibiotic use before ICU infection (OR=7.7, p=0.04), and arterial catheter (OR=2.8, p=0.03). The median antibiotic cost was significantly higher for patients in the case group [$663.50 (27–3,752) and $256.00 (0–2,716), respectively] (p<0.01). Also, a total hospital cost for patients was significantly higher in the case group ($8,895 [2,621–23,883] and $6,551 [1,441–20,425], respectively) (p<0.05).

**Conclusion:** Patients with a high APACHE II score transferred from another hospital and who use an antibiotic before the ICU infection and arterial catheter are at a greater risk of MDR-GN infections. Also, the infections pose a significant burden on health care facilities due to more prolonged and costly treatments.

**Keywords:** Economic burden, gram negatives, developing country

**Cite this article as:**
Ulu Kılıç A, Kalın Ünüvar G, Cevahir F, Alp E. Economic Burden of Multidrug-Resistant Gram-Negative Infections in a Developing Country. Erciyes Med J 2019; 41(3): 312-5.

[1]Department of Infectious Diseases, Erciyes University Faculty of Medicine, Kayseri, Turkey
[2]Infection Control Committee, Erciyes University Faculty of Medicine, Kayseri, Turkey
[3]Republic of Turkey, Ministry of Health, Ankara, Turkey

**Submitted**
18.03.2019

**Accepted**
27.06.2019

**Available Online Date**
19.08.2019

**Correspondence**
Ayşegül Ulu Kılıç,
Department of Infectious Diseases, Erciyes University Faculty of Medicine, Kayseri, Turkey
Phone: +90 0352 207 66 66 -22057
e-mail: draysegululuu@yahoo.co.uk



## INTRODUCTION

Antibiotic-resistant infections pose a significant global public health threat due to the rising prevalence and limited therapeutic alternatives. These infections are mostly associated with longer hospital stays, higher incidence of therapeutic complications, and a prolonged duration of treatment, therefore causing more costly patient care in health care settings (1, 2).

Gram-negative infections are particularly prominent in intensive care units (ICU). They receive more attention due to increasing resistance; furthermore, there are no new approved antimicrobials available for multidrug-resistant gram-negative (MDR-GN) pathogens. The clinicians have difficulty to manage the treatment with the existing antibiotics. Accordingly, using multiple wide-spectrum antibiotics had facilitated the cycle of increasing resistance. As another consequence of resistance, the treatment duration and hospital costs increased steadily with the need to use combined antimicrobial treatments and prolonged utilization of antibiotics for the resistant infections. Also, difficult-to-treat infections due to MDR-GN may severely impair the patient's quality of life due treatment ineffectiveness, and they even could be life threatening (3).

In this study, we investigated the risk factors for the acquisition of MDR-GN in the first ICU infection episode of patients and also calculated the economic burden of the first episode of infection with MDR-GNs that the ICU patient faced.

## MATERIALS and METHODS

This is a 1-year retrospective observational study conducted between 2016 and 2017 in a tertiary care center with a 1,300 bed capacity in central Turkey. The patients included in this study were hospitalized in four separate adult ICUs with a 55-bed capacity. The types of ICUs included the Medical, General Surgery, Neurosurgery and Anesthesiology, and Reanimation.

Hospital-acquired infections (HAIs) were defined according to the Centers for Disease Control and Prevention

National Healthcare Safety Network surveillance definitions (4). The case was defined as a patient who had an MDR-GN in their first episode of ICU infection, and control was defined as a patient who had a non-MDR-GN in their first episode of ICU infection. An MDR characteristic was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (5). Patients who had Candida or a gram-positive infection or without any isolated pathogens in their first episode were excluded. Patients who had any other overlapping infection due to an MDR-GN pathogen during this period were also excluded. Hospital infections occurred more than 48 hours later. The patients who were followed up with nosocomial infection were included in the first episode of MDR-GN bacteremia following ICU transfer.

An empirical antimicrobial treatment was defined as "inappropriate" if the receipt antimicrobial did not treat all organisms based on subsequent in vitro susceptibility tests, whereas "appropriate" treatment had a coverage that met these criteria.

The cost analysis per patient was calculated for the case and control groups (in constant US$ 2,016; Central Bank of the Republic of Turkey, December 30, 2016, 1 USD = 3.5255 Turkish Lira), retrospectively. Data on the costs were obtained using the hospital's accounting system. The median antibiotic and total health care costs of patients were included till the treatment of this first episode completed. Total health care costs included ICU bed charge, ventilator charge, and cost of drug therapy.

For risk factor analysis, demographic characteristics of patients (age, gender, comorbidity index), the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II Scoring, transfer from another unit, transfer from another hospital, community-acquired infection on admission, NI before the ICU admission, antibiotic use before ICU infection, time elapsed to the onset of the first episode of ICU infection, invasive procedures, and operations were evaluated.

A statistical analysis was performed using the SPSS software version 15.0 (IBM, Armonk, NY). The chi-squared or the Fischer exact test was used for categorical variables. The Shapiro–Wilk test was performed to check the normality assumption of the data. The Mann–Whitney U test was used to compare the differences between the two groups. Univariate and multiple binary logistic regression analyses (Backward stepwise selection) were performed to analyze the effects of variables (confidence interval, CI 95%). In the multiple logistic regression analysis, the variables found to be significantly associated with the MDR-GN infection in the univariate analysis were included. The level of significance was set at $p<0.05$ for all tests.

### Ethics

This research was approved by the Non-invasive Clinical Research Ethics Committee of Erciyes University (Date 05.08.2019, Number 2019/355).

## RESULTS

A total of 100 patients were included into the study. Thirty-six were hospitalized in the Medical ICU, 33 in General Surgery, 18 in Neurosurgery, and 13 in the Anesthesiology and Reanimation ICU. Sixty-two patients had MDR-GN, and 38 patients had a non-MDR pathogen in their first ICU infection episode. The mean age was 61.2±16.0 years, and 49% were male.

**Table 1.** Isolated microorganisms from the first ICU episode of infection of patients with and without MDR

| | MDR (n=66) | | Without MDR (n=44) | |
|---|---|---|---|---|
| | n | % | n | % |
| *Acinetobacter baumannii* | 37 | 56.1 | 0 | 0.0 |
| *Pseudomonas aeruginosa* | 9 | 13.6 | 8 | 18.2 |
| *Escherichia coli* | 5 | 7.6 | 10 | 22.7 |
| *Klebsiella pneumoniae* | 9 | 13.6 | 11 | 25.0 |
| *Enterobacter cloace* | 2 | 3.0 | 2 | 4.5 |
| *Stenotrophomonas maltophia* | 3 | 4.5 | 0 | 0.0 |
| *Proteus mirabilis* | 1 | 1.5 | 0 | 0.0 |
| *Klebsiella oxytoca* | 0 | 0.0 | 3 | 6.8 |
| *Pseudomonas* spp. | 0 | 0.0 | 2 | 4.5 |
| *Serratia marcescens* | 0 | 0.0 | 3 | 6.8 |
| *Enterobacter* spp. | 0 | 0.0 | 1 | 2.3 |
| *Pseudomonas putida* | 0 | 0.0 | 1 | 2.3 |
| Gram-negative basil | 0 | 0.0 | 2 | 4.5 |
| *Acinetobacter junii* | 0 | 0.0 | 1 | 2.3 |

ICU: Intensive care unit; MDR: Multidrug-resistant

Forty-one patients had pneumonia, 24 had urinary tract infection, 20 had bacteremia, 14 patients had a surgical site infection, and 1 patient had a skin–soft tissue infection. Ninety-four patients had monomicrobial infection, and 107 gram-negative microorganisms were isolated. Of case patients, the most prevalent GN infections were due to *A. baumannii* (56%), *P. aeruginosa* (14%), *K. pneumoniae* (14%), and *E. coli* (7.5%). In control patients, the most prevalent pathogens were *K. pneumoniae* (25.5%), *P. aeruginosa* (23.2%), and *E. coli* (23.2%) (Table 1). All *A. baumannii* isolates were extremely drug resistant.

In the univariate analysis APACHE II score, community-acquired infection, nosocomial infection before ICU, transfer from another hospital, antibiotic use before an ICU infection, and central venous and arterial catheter were significant risk factors. In a multivariate analysis, an APACHE II score, transfer from another hospital, antibiotic use before the ICU infection, and arterial catheter were the most significant risk factors for the MDR-GN ICU infection (Table 2). Mortality was 58% in cases and 39.5% in controls ($p=0.07$).

The median antibiotic cost was significantly higher for patients in the case group ($663.50 [27–3,752] and $256.00 [0–2,716], respectively) ($p<0.01$). Also, the total hospital cost for patients was significantly higher in the case group ($8,895 [2,621–23,883] and $6,551 [1,441–20,425], respectively) ($p<0.05$).

## DISCUSSION

MDR-GN bacteria have an increasing prevalence in most of the ICUs of health care settings. New and effective antibiotics are unavailable in most ICUs, especially in developing countries. The treatment of antibiotic resistant infections becomes more challeng-

**Table 2.** Demographic characteristics, severity criteria, invasive procedures, and mortality rate of patients with and without mdr-gn bacteria

| | MDR-GN (n=62) | | Without MDR-GN (n=38) | | p | Multivariate analysis OR (95% CI) | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | | | |
| Mean age (±SD) | 61.9±15.7 | | 60.1±17.8 | | 0.585 | | |
| Gender (male) | 35 | 56.5 | 16 | 42.1 | 0.164 | | |
| APACHE II median (min–max) | 19.5 (7–42) | | 15.0 (4–30) | | **0.032** | 1.087 (1.019–1.160) | **0.012** |
| Expected mortality rate median (min–max) | 35.5 (7.6–92.2) | | 26.3 (5.1–70.3) | | 0.058 | | |
| Comorbidity index median (min–max) | 5.0 (0–20) | | 4.5 (0–19) | | 0.776 | | |
| Days elapsed to the onset of infection median (min–max) | 9.5 (2–39) | | 6.0 (2–44) | | 0.121 | | |
| Length of hospitalization in days median (min–max) | 19.5 (5–131) | | 19.0 (3–94) | | 0.311 | | |
| Transfer from another ward | 41 | 66.1 | 21 | 55.3 | 0.277 | | |
| Transfer from another health care setting | 13 | 21.0 | 1 | 2.6 | **0.015** | 9.339 (1.097–79.481) | **0.041** |
| Nosocomial infection before ICU admission | 17 | 27.4 | 3 | 7.9 | **0.021** | | |
| Antibiotic use before ICU infection | 60 | 96.8 | 31 | 81.6 | **0.010** | 7.779 (1.166–51.917) | **0.034** |
| Appropriate empiric therapy | 22 | 41.5 | 11 | 50.0 | 0.500 | | |
| Trauma | 3 | 4.8 | 8 | 21.1 | **0.019** | | |
| Invasive devices and procedures | | | | | | | |
| Total parenteral nutrition | 21 | 33.9 | 16 | 42.1 | 0.408 | | |
| Enteral nutrition | 31 | 50.0 | 20 | 52.6 | 0.798 | | |
| Transfusion | 42 | 67.7 | 19 | 50.0 | 0.077 | | |
| Urinary catheter | 57 | 91.9 | 38 | 100 | 0.072 | | |
| Hemodialysis | 9 | 14.5 | 2 | 5.3 | 0.198 | | |
| Intubation/mechanical ventilation | 50 | 80.6 | 25 | 65.8 | 0.096 | | |
| Tracheostomy | 16 | 25.8 | 9 | 23.7 | 0.812 | | |
| Central venous catheter | 50 | 80.6 | 23 | 60.5 | **0.028** | | |
| Arterial catheter | 34 | 54.8 | 12 | 31.6 | **0.023** | 2.798 (1.091–7.180) | **0.032** |
| Drainage catheter | 23 | 37.1 | 13 | 34.2 | 0.770 | | |
| Foreign tools | 7 | 11.3 | 3 | 7.9 | 0.738 | | |
| Nasogastric tube | 44 | 71.0 | 27 | 71.1 | 0.993 | | |
| Operation | 24 | 38.7 | 15 | 39.5 | 0.939 | | |
| Mortality | 36 | 58.1 | 15 | 39.5 | 0.071 | | |

MDR GN: Multidrug-resistant gram negatives; CI: Confidence interval; SD: Standard deviation; ICU: Intensive care unit

ing and results in an increased risk of poor clinical outcomes for patients and higher costs for the health care institutions. In case of resistance to both old and novel agents, alternative treatment approaches such as the combination of two carbapenems, may be preferred in therapy. However, administering a combination of antibiotics may increase the adverse events and complications and burden health care costs (6).

The most common infections were found to be due to *A. baumannii* in this study, which is also defined as an extensively drug-resistant pathogen (XDR). Current studies from Saudi Arabia have also reported that the most commonly isolated pathogens were *Acinetobacter* spp. (27.2%) followed by *P. aeruginosa* (23.8%) and *K. pneumoniae* (18.6%). The range of antimicrobial resistance (except colistin) was 97.5% for *Acinetobacter* spp. (7). Colistin is an old drug that emerged for the treatment of resistant gram negatives. It is cheap in price but has serious side effects such as nephrotoxicity, which affects the hospital costs, as well as morbidity and mortality.

Several risk factors have been previously identified that affect the acquisition of MDR-GN bacteria (8). In accordance with the results of previous studies, patients who have a high APACHE II score are found more likely to have an MDR infection episode. The reason is thought to be the need of longer periods and a wider spectrum of antibiotics for this subpopulation of patients. Also, patients receiving an arterial catheterization are more likely to have a higher severity of illness scores, and so it has been found to be significantly associated with the acquisition of MDR-GN bacteria in this present study.

A transfer from another health care setting was also found to be a significant risk factor for an infection with MDR-GN bacteria (9). Patients who have a history of transfer from another health care institution and long-term care facilities are more likely to acquire the colonization and infection with resistant microorganisms. Screening and isolation policies should be implemented strictly for patients particularly with a history of admission to health care settings with known endemic MDR-GN infections.

A cross transmission of MDR-GN pathogens has been shown to occur frequently in hospitals. Multidisciplinary efforts are needed to control spreading of these organisms; thus, increasing costs due to the MDR-GNs treatment can be avoided. Education to improve adherence to hand hygiene practices and use of contact precautions has been shown as beneficial in reducing the cross transmission of resistant bacteria in several studies (10).

Both total hospital costs and antibiotic costs were found to be higher in patients with MDR-GN infections in this present study. This result does not seem to be associated with the prolonged hospital stay of case patients because it was found to be similar in both groups. The probable cause may be the use of more expensive antibiotics and their combination in this group of patients. Also, patients with an MDR infection in the first episode who are critically ill have a median APACHE score of almost 20. The treatment of serious complications in these patients may have also caused an increased cost.

The major limitation of this study is that we could not include data for patients retrospectively, such as the type of antibiotics used and burden of complications that may affect hospital costs.

In conclusion, MDR-GN bacterial infections place a significant burden on health care facilities due to more prolonged and costly treatments. Forecasting the acquisition of resistant infections properly and initiating appropriate empirical therapy will have a favorable outcome on the survival of patients and thus reduce the hospital costs.

**Ethics Committee Approval:** This research was approved by the Non-invasive Clinical Research Ethics Committee of Erciyes University (Date 08 /05/2019, Number 2019/355).

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – AUK, EA; Design – AUK, EA; Supervision – EA; Resource – AUK, EA; Materials – AUK, EA; Data Collection and/or Processing – FC; Literature Search – AUK; Writing – AUK, GKÜ; Critical Reviews – AUK.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## REFERENCES

1. Giske CG, Monnet DL, Cars O, Carmeli Y; ReAct-Action on Antibiotic Resistance. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrob Agents Chemother 2008; 52(3): 813–21. [CrossRef]
2. Cerceo E, Deitelzweig SB, Sherman BM, Amin AN. Multidrug-Resistant Gram-Negative Bacterial Infections in the Hospital Setting: Overview, Implications for Clinical Practice, and Emerging Treatment Options. Microb Drug Resist 2016; 22(5): 412–31. [CrossRef]
3. Siwakoti S, Subedi A, Sharma A, Baral R, Bhattarai NR, Khanal B. Incidence and outcomes of multidrug-resistant gram-negative bacteria infections in intensive care unit from Nepal- a prospective cohort study. Antimicrob Resist Infect Control 2018; 7: 114. [CrossRef]
4. Centers for Disease Control and Prevention/ National Healthcare Safety Network. CDC/ NHSN Surveillance Definitions for Specific Types of Infections. January 2017. Available from: URL: https:// www.cdc.gov/ nhsn/ pdfs/ pscmanual/ 17pscnos infdef_current.pdf.
5. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18(3): 268–81. [CrossRef]
6. Oliva A, Giacobbe DR, Di Luca M, Miller NS. New Insights into Infections due to Multidrug Resistant Gram Negative Bacteria: The Interplay between Lab and Clinic. Biomed Res Int 2018; 2018: 8905874.
7. Ibrahim ME. High antimicrobial resistant rates among Gram-negative pathogens in intensive care units. A retrospective study at a tertiary care hospital in Southwest Saudi Arabia. Saudi Med J 2018; 39(10): 1035–43. [CrossRef]
8. Thaden JT, Li Y, Ruffin F, Maskarinec SA, Hill-Rorie JM, Wanda LC, et al. Increased Costs Associated with Bloodstream Infections Caused by Multidrug-Resistant Gram-Negative Bacteria Are Due Primarily to Patients with Hospital-Acquired Infections. Antimicrob Agents Chemother 2017; 61(3).pii: e01709–16. [CrossRef]
9. Ulu-Kilic A, Alp E, Percin D, Cevahir F, Altay-Kürkçü C, Ozturk A, et al. Risk factors for carbapenem resistant *Klebsiella pneumoniae* rectal colonization in pediatric units. J Infect Dev Ctries 2014; 8(10): 1361–4.
10. Halaby T, Al Naiemi N, Beishuizen B, Verkooijen R, Ferreira JA, Klont R, et al. Impact of single room design on the spread of multi-drug resistant bacteria in an intensive care unit. Antimicrob Resist Infect Control 2017; 6: 117. [CrossRef]