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# The Effect of Antimicrobial Policy Implementation on Carbapenem Resistance: A University Hospital Experience

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## ABSTRACT

**Objective:** The resistance of Gram-negative bacteria to antibiotics is a global issue that leads to increased mortality and treatment costs. The aim of this study is to see how a newly formed carbapenem control team affected the prevalence of carbapenem-resistant Gram-negative rods and antibiotic consumption expenses in 2017 compared to the year before.

**Methods:** The rate of carbapenem antibiotic usage in Intensive Care Units and Bone Marrow Transplantation services, as well as the findings of culture materials obtained from various body parts of the same patients, between January 1, 2016, and December 31, 2017 were assessed.

**Results:** While there was an ordinary restriction on carbapenem consumption in 2016, carbapenem consumption has been more restricted in 2017. The carbapenem-resistant Gram-negative bacteria patterns of culture materials are examined and compared with Defined Daily Dose data of carbapenems. After the restriction, a significant decrease in the consumption of carbapenems was detected. The decline in carbapenem-resistant Gram-negative bacteria and decreasing antibiotic consumption were found to have a moderately positive correlation ($r=0.641$, $p=0.02$). A 60.9% decrease was observed in carbapenem costs after carbapenem restriction, on the other hand, an increase in other unrestricted antibiotics was apparent.

**Conclusion:** Antimicrobial restriction policies can help minimize the rate of carbapenem-resistant Gram-negative rods, which is a serious problem in healthcare. We demonstrated that a decrease in carbapenem-resistant Gram-negative rods isolation rates can lead to a decrease in healthcare-associated infections. Although there is no decrease in the direct antibiotics cost, a drop in carbapenem-resistant may lower the expenses of drastic consequences of infections with carbapenem-resistant and its cost. we can conclude that the Antibiotic Control Policy should be modified based on this new information.

**Keywords:** *Carbapenem, Resistance, Gram-Negative Bacteria*

## 1. INTRODUCTION

Antibiotics are among the most important medications used in healthcare today, yet their inappropriate usage has resulted in major problems such as Antimicrobial Resistance. In 2018, Irrational antibiotic use was reported in many hospitals, according to a cross-national study that included Eastern Europe and Central Asia, with Turkey ranking as one of the largest consumers of systemic antimicrobials (1).

The global antibiotic consumption rate is estimated to be 14.3 defined daily doses (DDD) per 1000 population per day in 2018, a 46 percent increase from 2000 (2). In 2011, data on antimicrobial use in 13 non-European Union countries ranged from 15.3 to 42.3 defined daily dose/1000 inhabitants per day (DID), including Turkey (42.3 DID), with data from Turkey limited to outpatient use (3). A recent systematic review that measured the point prevalence and inappropriate antibiotic prescription in Turkey highlighted high consumption rates and inappropriate antibiotic use over the last 15 years, necessitating the implementation of strict and effective stewardship in all Turkish hospitals (4). Antimicrobial restriction policies are intended to reduce morbidity and mortality, as well as the expense of treatment, the length of hospitalization, and the rate of resistance microorganisms, while also improving quality of life (5-6).

Gram-negative rods (GNRs) are among the most frequent causes of community-acquired and healthcare-related infections. The consumption of antibiotics excessively and unnecessarily came along with emerging antimicrobial resistance. Carbapenem group antimicrobials are the last resort to treat multidrug-resistant (MDR) GNRs until recent years(7). Overuse of carbapenems resulted in carbapenem resistance (CR) in *Enterobacterales* especially *Klebsiella* spp (8, 9). In the last ten years, reports of an increase in the incidence of carbapenem-resistant Gram-negative rods (CRGNR) infections such as urinary tract, bloodstream, and ventilator-associated pneumonia, as well as the rate of



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colonization with these microbes, have been reported in the hospital setting studies (10-12). These infections can be seen as sporadic cases or hospital outbreaks. Unfortunately, in addition to their higher toxicity, such as nephrotoxicity, the therapy choices for infections caused by CRGNRs are severely limited. More effective and less toxic agents have been introduced into clinical practice in recent years, although widespread use is still not available in most countries. Thus controlling the emergence and spread of carbapenem resistance and rational use of antimicrobials is essential for the prevention of such infections and their severe complications(11, 12). In Turkey, the antibiotic restriction policy and Rational Drug Use National Action Plan were implemented in 2003 and 2014, respectively(13-16). These actions resulted in decreasing restricted antibiotic consumption by 26.7% while increasing unrestricted antibiotics and decreasing the prevalence of extended-spectrum beta-lactamase-producing *K. pneumoniae* (17, 18). GNRs are opportunistic pathogenic microorganisms that cause epidemics in hospital settings, particularly in ICUs. Inappropriate antibiotic use in hospitals has led to the development of resistance to many antibiotics used in GNRs. Carbapenem consumption has an important place in various resistance mechanisms. This study aims to see how a newly formed carbapenem control team affected the prevalence of carbapenem-resistant Gram-negative rods and antibiotic consumption expenses in 2017 compared to the year before at Medipol Mega University Hospital in 2017.

## 2. METHODS

We planned a quasi-experimental study and aimed to evaluate the effect of the newly established carbapenem (imipenem-cilastatin, meropenem, ertapenem) control team (infectious diseases specialist, clinical pharmacist, and infection control nurse) on the antibiotic policy of our hospital on the resistance pattern of GNRs and costs of total antibiotic consumption. Two different annual periods were analyzed. The first one was between Jan-Dec 2016 (Group 1) which there was no restriction or intervention except standard antibiotic policies and the latter was between Jan-Dec 2017 (Group 2) which was intervened by the carbapenem control team after training healthcare staff in the included departments. The carbapenem restriction was made by setting a carbapenem-team approval system in the intervention period. Our center is a third-level university hospital settled in Istanbul and has 515 beds. All ICUs have 104 beds (Adult ICU, Cardiovascular Surgery ICU, and neonatal ICU) and bone marrow transplantation units have 25 beds (adult and pediatric) all of them were included in the study. Coronary ICU was not included because of the short hospitalization period and no carbapenem use. The study included all hospitalized patients in these departments over the specified time periods who were given carbapenems and found CR GNRs in their various samples, regardless of whether they were infected or colonized. In the event of clinical necessity, samples were obtained after consulting with an infectious diseases specialist. Patients who have a history of prior hospitalization and carbapenem use or were found carbapenem-resistant Enterobacteriaceae (CRE) in the screening cultures were excluded.

The ethics committee of Medipol University gave their consent (NO: 328, Date: 15.09.2017), as well as the institution's permission. All data (culture results, hospitalization days, antibiotic consumption amount) was obtained from the hospital information system. The unit price of antibiotics was calculated based on the Turkish Drug Guidelines list. Antibiotic consumption index (ACI) was calculated based on ATC/DDD method suggested by World Health Organization (WHO).

$$ACI = \frac{Total\ amount\ of\ antimicrobial\ used}{DDD * Hospitalized\ days} \chi 1000$$

With this study, we set out to address three main questions: (1) Are the CR GNRs rates going to decrease after intervention? (2) Is the consumption of carbapenems going to decrease after intervention? (3) Is there any effect of the intervention to decrease the consumption of antibiotics other than carbapenems?

Descriptive statistics and the compliance of variables to normal distribution were examined in the study. Shapiro-Wilk test was performed to assess the normality of frequencies. Paired samples t-test was used to compare normally distributed data. Spearman correlation analysis was used to examine the relationship between the resistant number by years and the amount of consumption per patient. Mann-Whitney U test was used to compare inpatients, patient days, urinary catheter days, ventilator days, and central catheter days by years. The chi-square test was used to compare qualitative data. Results of quantitative data are given in mean ± standard deviation/median (min-max) and qualitative data are also presented as frequency and percentage. The significance level was set at p<0.05.

## 3. RESULTS

A total of 1604 samples were taken and cultured within both annual periods. A total of 680 CR GNRs were isolated eventually. Demographic and descriptive characteristics of groups were given in Table 1.

**Table 1** Demographic and descriptive characteristics of groups

| | Group 1 | Group 2 | Total | P |
|---|---|---|---|---|
| Age | 47.5 (12-73) [0-98] | 53 (23-68) [0-96] | 51 (21-70) [0-98] | N/A |
| Gender (M/F) | 171/113 (60/40) | 162/99 (62/38) | 333/212 (61/39) | N/A |
| Admitted patients N (%) | 47 (23.5 – 69.3) | 63.5 (20.5 – 74) | | 0.6 |
| Hospital-Days | 450 (267-540) | 452 (251 – 544.5) | N/A | 0.6 |
| Urinary catheter days | 72 (0-331) | 61 (0-341.8) | N/A | 0.9 |
| Ventilator Days | 194 (0-308) | 206 (0-355) | N/A | 0.6 |
| Central Catheter Days | 221 (152-277) | 235 (153-294) | N/A | 0.5 |
| ACI – Carbapenem Class per patient | 2239.94 ± 104.056 | 853.64 ± 215.16 | N/A | **<0.00** |

Data was given in median (IQR) [Min-Max] or N (%) or Mean±SD. Group 1: Jan-Dec 2016 with no intervention; Group 2: Jan-Dec 2017 after intervention; ACI: Antibiotic consumption index

The most common GNRs found in culture materials taken before the intervention was *Acinetobacter* spp. 149 (96%) *Klebsiella* spp. 151 (48%), *Pseudomonas aeruginosa* 88 (47%) while after intervention it was *Acinetobacter* spp. 131 (92%), *Pseudomonas aeruginosa* 72 (40%) *Klebsiella* spp. 56 (25%), in order. It was found that GNRs isolation rates (mean ± SE: 34±3 vs 23±3) after intervention decreased (p= 0.012). The number of isolated Gram-negative bacilli was given in Table2.

**Table 2** Number of isolated Gram-negative bacilli.

| | Months | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **Total** |
| **Group 1** | **36** | **34** | **36** | **46** | **37** | **21** | **47** | **44** | **19** | **26** | **32** | **33** | **411** |
| *Acinetobacter spp.* | 10 | 15 | 16 | 10 | 15 | 3 | 19 | 22 | 8 | 9 | 11 | 11 | 149 |
| *Enterobacter spp* | | | 1 | 3 | 6 | 3 | 2 | 1 | | | | | 16 |
| *Escherichia coli* | | 1 | | 1 | | 1 | | | | | | 1 | 4 |
| *Klebsiella spp.* | 14 | 13 | 13 | 23 | 11 | 12 | 17 | 8 | 7 | 7 | 15 | 11 | 151 |
| *Morganella spp.* | | | | | | | | | | | | 1 | 1 |
| *Proteus mirabillis* | | | | | | | 1 | | | | | 1 | 2 |
| *Pseudomonas aeruginosa* | 12 | 5 | 6 | 9 | 5 | 2 | 8 | 13 | 4 | 10 | 6 | 8 | 88 |
| **Group 2** | **49** | **17** | **10** | **23** | **25** | **15** | **14** | **17** | **19** | **27** | **26** | **27** | **269** |
| *Acinetobacter spp.* | 21 | 3 | 4 | 15 | 20 | 9 | 6 | 10 | 8 | 11 | 13 | 11 | 131 |
| *Enterobacter spp* | | 1 | | | | | 1 | | | | 2 | 1 | 5 |
| *Escherichia coli* | 2 | 1 | | | | | | | | | 1 | 1 | 5 |
| *Klebsiella spp.* | 15 | 5 | 5 | 4 | | 1 | 4 | 3 | 2 | 10 | 4 | 3 | 56 |
| *Proteus spp* | | | | | | | | | 1 | | 1 | 1 | 3 |
| *Pseudomonas aeruginosa* | 11 | 7 | 1 | 4 | 5 | 5 | 3 | 4 | 8 | 6 | 4 | 10 | 72 |
| *Serratia marcescens* | | | | | | | | | | | 1 | | 1 |
| **Total** | **85** | **51** | **46** | **69** | **62** | **36** | **61** | **61** | **38** | **53** | **58** | **60** | **680** |

Different types of samples were evaluated, carbapenem-resistant GNRs occurrence in blood cultures and bronchoalveolar lavage samples were reduced (Table 3). Aside from that, there were no significant differences.

While the average amount of expenditure before the intervention was 67.927 Turkish Lira (TL), it was 76.554 TL after the intervention, with no statistically significant difference between the median values (p> 0.05). While the total amount of spending before the restriction was 10.089.963 TL, the total amount of spending after the restriction was 7.376.913 TL. Following carbapenem restriction, costs for carbapenem, lincosamides, and first-generation cephalosporins decreased by 60.9%, 56.3%, and 51.5%, respectively, while costs for second-generation cephalosporins, macrolides, penicillin, and beta-lactamase inhibitors increased by 61.9%, 52.7%, and 48.9%, respectively.

**Table 3** Carbapenem resistant Gram negative rods isolated from culture materials.

| Sample | Group | Resistant n (%) | Sensitive n (%) | $X^2$ | P |
|---|---|---|---|---|---|
| **Blood** | **G 1** | 108 (58) | 117 (52) | 16.465 | **0.001*** |
| | **G 2** | 63 (29.2) | 153 (70.8) | | |
| **Abscess** | **G 1** | 2 (66.7) | 1 (33.3) | - | - |
| | **G 2** | 1 (50) | 1 (50) | | |
| **Bronchoalveolar lavage** | **G 1** | 28 (63.6) | 16 (36.4) | 7.582 | **0.006*** |
| | **G 2** | 26 (35.6) | 47 (64.4) | | |
| **Sputum** | **G 1** | 29 (63) | 17 (37) | 0.007 | 0.933 |
| | **G 2** | 8 (57.1) | 6 (42.9) | | |
| **CSF** | **G 1** | 4 (100) | 0 | - | - |
| | **G 2** | 0 | 1 (100) | | |
| **Tissue Biopsy** | **G 1** | 4 (44.4) | 5 (55.6) | 0.525 | 0.301 |
| | **G 2** | 1 (20) | 4 (80) | | |
| **Urine** | **G 1** | 27 (26.5) | 75 (73.5) | 0.183 | 0.669 |
| | **G 2** | 14 (22.2) | 49 (77.8) | | |
| **Catheter tip** | **G 1** | 30 (57.7) | 22 (42.3) | 0.776 | 0.379 |
| | **G 2** | 21 (46.7) | 24 (53.3) | | |
| **Endotracheal aspirate** | **G 1** | 147 (49) | 153 (51) | 2.719 | 0.12 |
| | **G 2** | 109 (42.4) | 148 (57.6) | | |
| **Sterile fluid** | **G 1** | 14 (50) | 14 (50) | 1.751 | 0.186 |
| | **G 2** | 11 (30.6) | 25 (69.4) | | |
| **Wound swab** | **G 1** | 18 (50) | 18 (50) | 1.272 | 0.259 |
| | **G 2** | 15 (34.9) | 28 (58.2) | | |

The difference in carbapenem class antibiotic consumption index (ACI) between the two groups was statistically significant (Table 1), and carbapenem class antibiotic restriction was moderately correlated with a decrease in CR GNR isolation rate (r=0.641, p=0.02).

## 4. DISCUSSION

Carbapenem class antibiotics are potent options for extended-spectrum beta-lactamases. ESBL producing GNRs yet increasing carbapenem resistance limits its efficacy in daily clinical practice (19). Our findings of frequently isolated GNRs were *Acinetobacter* spp. (96%), *Klebsiella* spp. (48%) and *Pseudomonas aeruginosa* (47%). This finding is similar to what has been found in other ICUs (20-22). The difference of means of annual isolated carbapenem-resistant strains in the non-carbapenem restricted and carbapenem restricted periods was statistically significant in our study. In a 12-year study, Ogutlu et al. concluded that intermittent carbapenem restriction had a significant impact on carbapenem resistance in *Acinetobacter spp* (23).

Our finding of decreased CR of GNRs isolated in blood and bronchoalveolar lavage fluid cultures after restriction of carbapenems, is supported by a multi-center study conducted between 2001-2005, and published in 2011. Altunsoy et al analyzed antimicrobial susceptibility of 14.223 blood culture isolates and antibiotic consumption rate. They found that carbapenem restriction has a considerable role in the reduction of carbapenem-resistant Pseudomonas spp. and *Acinetobacter spp* (24). In our study, carbapenem restriction via an ID approval system resulted in a significant reduction in ACI. Similarly, Inan et al. discovered that ID consultation improves rational antibacterial selection (25). Another study found that analyzing prospective active surveillance data before and after antimicrobial use reduced antibiotic use and promoted rational antimicrobial use (26). According to a Saudi Arabian study, a three-month carbapenem-free period reduced Pseudomonas aeruginosa meropenem resistance from 74.1 percent to 30 percent and imipenem resistance from 76 percent to 38.5 percent (p=0,01) in comparison to the previous three months. Therefore this research may conclude that, even short-term carbapenem restriction periods may interfere with carbapenem resistance in Pseudomonas aeruginosa, (PSA) (27). Pakyz et al. studied the effects of carbapenem restriction implementation on carbapenem-resistant PSA in 22 university hospitals in the United States of America. In the study, the period from 2002 to 2006 was evaluated retrospectively and it was reported that significantly less carbapenem was consumed in 8 hospitals while carbapenem restriction was implemented (p = 0.04) and significantly lower isolation rate of carbapenem-resistant PSA (p = 0.01) (28). As a result, it has been shown that carbapenem restriction can reduce carbapenem resistance rates in Pseudomonas aeruginosa.

In our study, after carbapenem restriction, 60.9% reduction in the cost of carbapenem use, 56.3% in lincosamides, and 51.5% in 1$^{st}$ generation cephalosporins were observed, yet the cost of second-generation cephalosporins 61.9%, macrolides 52.7%, and Penicillin and beta-lactamase inhibitors increased by 48.9%. According to Arda et al., the adoption of an antimicrobial approval system resulted in a 19.6% reduction in total antibiotic expenditures in the restricted antibiotic groups, but an increase in unrestricted antibiotics (18). A point prevalence survey conducted by Özgenç et al. in 8 universities training and research hospitals in the Aegean region, found that the rate of rational antibiotic use of antibiotics was significantly higher because of the antibiotic restriction practices (29). According to all these studies conducted in our country, antibiotic consumption rates, as well as the expenses of various resistant microbes and antibiotic costs, can be lowered when antibiotic restriction policies are implemented.

## 5. CONCLUSION

Antimicrobial restriction policies can help minimize the rate of CR GNRs, which is a serious problem in healthcare. We demonstrated that a decrease in CR GNRs isolation rates can lead to a decrease in healthcare-associated infections. Although there is no decrease in the direct antibiotics cost, a drop in CR may lower the expenses of drastic consequences of infections with CR and its cost. Antimicrobial stewardship based on ID consultation, limitation regulations, and local epidemiologic data results in reasonable antibiotic usage and superior clinical practices.

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