

1-1-2018

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KARABAY, OĐUZ; KAYA, GÜLSÜM; GÜÇLÜ, ERTUĐRUL; and ÖĐÜTLÜ, AZİZ (2018) "Positive effect of restrictions on antibiotic consumption," *Turkish Journal of Medical Sciences*: Vol. 48: No. 2, Article 23.

<https://doi.org/10.3906/sag-1709-133>

Available at: <https://journals.tubitak.gov.tr/medical/vol48/iss2/23>

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Positive effect of restrictions on antibiotic consumption

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Received: 25.09.2017 • Accepted/Published Online: 07.02.2018 • Final Version: 30.04.2018

Background/aim: This study aimed to examine the change in the etiology of hospital infections with restricting and releasing of group 2 carbapenems (G2C) (meropenem/imipenem/doripenem).

Materials and methods: This study was planned in three periods. Study period 1 (SP-1): Carbapenems were prescribed without restriction by infectious disease specialists. SP-2: G2C prescription was restricted. SP-3: Carbapenem prescription was released.

Results: In total, 4443 cases [1053 in SP-1 (23.7%), 1332 in SP-2 (29.9%), and 2085 in SP-3 (46.9%)] were included in the study. Infection rates were 11%, 6.5%, and 7.9% in SP-1, SP-2, and SP-3, respectively ($P = 0.001$). *Acinetobacter* spp.-related hospital infection rates were 3.9%, 1.2%, and 1.8%, in SP-1, SP-2, and SP-3, respectively ($P = 0.0001$). Infection related mortality in SP-1, SP-2, and SP-3 was 7.3%, 5%, and 3.8%, respectively ($P = 0.001$).

Conclusion: Hospital-acquired *Acinetobacter* infections, antibiotic consumption, and infection-related mortality were decreased significantly with the restriction of G2C. Positive behaviors that were obtained during the restricted period were continued with release of restriction.

Key words: Restriction of carbapenem, antibiotic stewardships, hospital-acquired *Acinetobacter* infections, infection related mortality

1. Introduction

Antibiotics are some of the most important drugs of the last century. However, the treatment of drug-resistant infections is quite difficult nowadays. The unnecessary use of antibiotics led to the increase and spread of multidrug-resistant bacteria (1). The use of antibiotics, treatment costs, and antibacterial resistance are lower in countries in which there is rational antibiotic consumption (2,3). By contrast, in countries in which there is no control over the use of antibiotics, both resistant microorganisms and infections caused by these resistant microorganisms increase more and more (4).

Acinetobacter baumannii, a nonfermentative and gram-negative bacterium, attracts attention due to its multidrug resistance. It causes significant nosocomial infections, especially in intensive care units (ICUs) (5). In recent years, reports of hospital infections caused by multidrug resistant *Acinetobacter baumannii* have been on the rise (6,7). Lately, a lot of *Acinetobacter*-related infections have been reported in Turkey. Carbapenem resistance in *Acinetobacter baumannii* infections has increased over the years and reached 90.7% in 2014 (8).

The use of carbapenem in our hospitals is quite excessive (9). The relationship between carbapenem use and resistant *Acinetobacter* has been investigated by many researchers (10). The reduction in the nonfermentative gram-negative bacilli colonization/infection by restricting carbapenem has been shown in many studies (4,11). In the first part of this study, we published the effect of carbapenem restriction on *Acinetobacter* epidemiology in ICUs (10). In the current study, we added a new and different period, and extended the duration of the second period of the first study. In the second part of the study, we aimed to investigate the effect of removing the restriction on physician behavior, mortality, G2C consumption, changes in antibiotic use between restriction and restriction-free period, and its effect on resistant *Acinetobacter* infections.

2. Materials and methods

2.1. Study design and data collection

This study was conducted at the Sakarya University Education and Training Hospital. The hospital has three separate campuses. There are a total of 956 patient beds in these campuses and 137 of them are in the ICU. This

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study was carried out over three periods on 25 beds of the anesthesia and reanimation ICU (ARICU) and 9 beds of the neurology ICU (NICU), between May 2011 and December 2015. All patients in these ICUs were followed daily by infectious disease and clinical microbiology specialists (IDCMS). In each period, similar infection control measures were performed. All data were obtained from patient files retrospectively.

Infection-related mortality for each period was calculated as patients who died after hospital infection diagnosis divided by number of patients hospitalized in the ICU during the same period.

2.2. Antibiotic prescription

Antibiotics were divided into two groups due to reimbursement restrictions in Turkey: restricted antibiotics (reimbursed when prescribed only by infectious disease specialists) and unrestricted antibiotics (reimbursed when prescribed by any doctor). Restricted antibiotics were imipenem, meropenem, doripenem, ertapenem, vancomycin, teicoplanin, daptomycin, linezolid, colistin, piperacillin/tazobactam, sulbactam, cefepime, cefoperazone/sulbactam, intravenous quinolones, and tigecycline.

Sakarya University Education and Training Hospital has a hospital information management system. Antibiotics were prescribed only by IDCMS, according to legal regulations in Turkey.

2.3. Study periods

The study was conducted in three periods. All patients were examined in the ICU before antibiotic prescription during all periods.

Study period 1 (SP-1): May 2011–February 2012

During this period, G2C was prescribed by IDCMS working in the hospital without restriction.

Study period 2 (SP-2): May 2012–September 2013

The use of G2C in SP-2 was restricted either in empirical use or after obtaining antibiogram results. According to the antibiogram results, G2C was not used if there was a chance of using other antibiotics other than G2C. Ertapenem, a carbapenem outside G2C, was prescribed freely.

Study period 3 (SP-3): October 2013–December 2015

During this period, G2C restriction was removed and IDCMS represcribed all carbapenems without any restriction for patients in need. In other words, antibiotic prescription rules returned to the rules in SP-1.

2.4. Antibiotic consumption data

The consumption of all antibiotics was obtained on a box basis from the data on the hospital information management system. According to the definition of daily defined dose (DDD) reported by the World Health Organization, antibiotics are transformed into value of DDD (12).

2.5. Inclusion criteria

All patients who were treated in ARICU and NICU in our hospital were included in the study. Infection and colonization were determined according to the Centers for Disease Control (CDC) hospital infection diagnostic criteria as defined elsewhere (13).

2.6. Exclusion criteria

Patients who were under 18 years old were excluded from the study.

2.7. Infection control procedures

Infection control procedures include avoiding use of unnecessary invasive applications, compliance to aseptic and antiseptic procedures during medical practice, removal of unnecessary invasive devices as soon as possible, and compliance with hand hygiene. These procedures were implemented during all study periods (14). Necessary cultures were obtained from patients in terms of fever, any changes in general condition, and suspicion of infection in the ICU.

2.8. Ethical approval

The ethical approval for this study was obtained from the Sakarya University Faculty of Medicine Ethics Committee on 23 December 2014 (No: 71522473/050.01.04/1).

2.9. Statistical analysis

Data were evaluated using the computer program Epi-info (CDC, Atlanta, GA, USA). Student's t-test was used to evaluate the quantitative variables; chi-square and Yates corrected chi-square tests were used to evaluate the qualitative data. $P < 0.05$ was considered significant.

3. Results

This study was carried out during three periods: 1053 patients were tracked during SP-1, 1322 patients were tracked during SP-2, and 2085 patients were tracked during SP-3. Patient and microbiological data are summarized in the Table.

Among the study periods, SP-2 had the lowest hospital infection rate [11.4% during SP-1, 6% during SP-2, and 7.8% during SP-3 ($P < 0.001$)]. The density of hospital infections during SP-1 = 19.6; during SP-2 = 7.6, and during SP-3 = 7.1 ($P < 0.001$).

The consumption amount of antibiotics is shown in Figure 1. While there was a significant difference in antibiotic consumption between SP-1 and SP-2 ($P = 0.01$), there was no difference between SP-2 and SP-3 ($P > 0.05$) (Figure 1).

The distribution of antibiotic consumption according to study periods is given in Figure 2. In the restriction period of G2C, the use of certain antibiotics (piperacillin/tazobactam and colistin) has increased.

The distribution of pathogens is given in Figure 3. While a significant difference was found in terms of

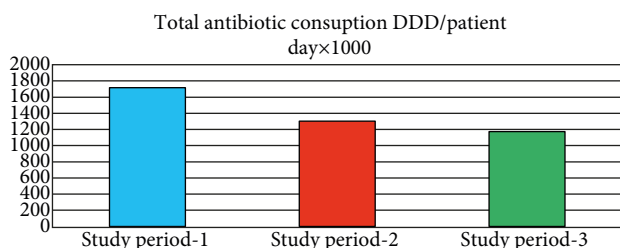


Figure 1. Antibiotic consumption according to periods.

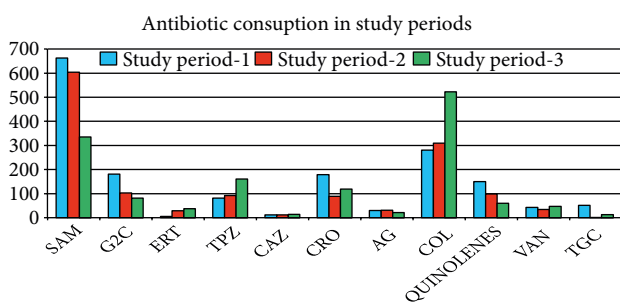


Figure 2. Distribution antibiotics used during study periods (DDD/patient day × 1000).

SAM: ampicillin/sulbactam; G2C: group 2 carbapenem; ERT: ertapenem; TZP: piperacillin/tazobactam; CAZ: ceftazidime; CRO: Ceftriaxone; AG: aminoglycosides; COL: Colistin; VAN: Vancomycin; TGC: Tigecycline.

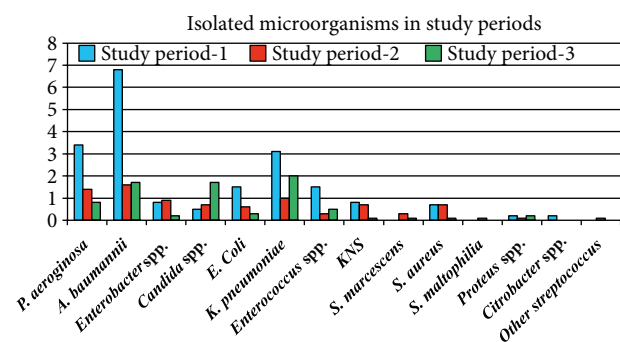


Figure 3. Distribution of bacterial agents.

Acinetobacter, *Klebsiella*, *Pseudomonas*, and *Candida*, there was no difference among the others.

Infection-related mortality was 7.3% during SP-1, while it was 5% ($P = 0.02$, OR: 1.49) during SP-2, and 3.8% during SP-3 ($P < 0.001$) (Table).

4. Discussion

Resistant infections are one of the leading causes of mortality in the ICU (15,16). Many strategies have been tried to deal with this problem (17). In one of these strategies, antibiotic stewardships have been applied, i.e. limited use of antibiotics, rational use of antibiotics, and use of antibiotics with rotation (18). The usage of broad spectrum antibiotics has caused collateral damage in the

hospital bacterial flora. Limitation of broad spectrum antibiotic usage in a hospital may decrease the percentage of antibiotic-resistant bacteria. We hypothesized that antibiotic restriction during defined periods can change hospital infection pathogens in the ICU as well as physician behaviors. Moreover, antibiotic rotation strategies are needed to reduce antimicrobial resistance. For this reason, we have used this strategy in our hospital for more than 8 years.

In this study, antibiotic restriction and later removal of the restriction have been investigated to determine what kind of behavior it causes in physicians who prescribe antibiotics (19). The study consisted of three periods. Carbapenem was used freely for 10 months (SP-1). After this period, G2C was restricted for 17 months (SP-2), and then all carbapenem prescription was released again for 27 months (SP-3). According to the basic results of this study, there was a decrease in the frequency of *Acinetobacter*, *Pseudomonas*, and *Klebsiella* spp.-related infections during the restricted period. Moreover, the usage of broad spectrum antibiotics during the restricted period and during the released restriction period decreased as well. After releasing the restriction, consumption of G2C did not increase, without any change in infection-related mortality.

The most striking finding of this study is that reduction in antibiotic consumption with restriction continues to decrease even when the restriction is removed. The use of G2C continued to decline both during the period of restriction and during the release of the restriction. In contrast, both during the restriction period and during the releasing of the restriction period, the use of colistin, piperacillin/tazobactam, and ertapenem increased. The increase in colistin consumption might be related to G2C limitation. Clinicians may choose to prescribe colistin during the G2C period due to antipseudomonal and anti-*Acinetobacter* effect of colistin. Increased use of colistin in the SP-3 may be related to habits gained with colistin use. Interestingly, quinolone consumption decreased without restriction. In ICUs in our center, quinolones are generally used in combination with G2C. We think that physicians who cannot use G2C during the restriction period do not include quinolones in the treatment either. Therefore, the restriction of carbapenems might reduce consumption of combined drugs such as quinolones or aminoglycosides as well.

Although all antibiotic restrictions were removed in SP-3, it was observed that the doctors who have the ability to prescribe any antibiotic freely continue to restrict themselves. During this period, while IDCMS were able to prescribe G2C, they still did not do so. We think that this can depend on the belief that treatments that do not contain G2C are as successful as those that do. Moreover,

Table. Hospital infections and Acinetobacter-related infection rates according to working periods.

Explanation	Study period 1 n (%) (density ‰)	Study period 2 n (%) (density ‰)	Study period 3 n (%) (density ‰)	P-value
Patients (n)	1053	1322	2085	
Patient days (n)	6143	10444	22827	
Hospital infections (n)	121 (11.4) (19.6)	80 (6.0) (7.6)	164 (7.8) (7.1)	0.0001
Ventilator-associated pneumonia	56 (5.3) (18.9)	32 (2.4) (6.1)	13 (0.6) (1.1)	0.001
Urinary catheter-related urinary tract infection	23(2.1) (4.0)	7 (0.5) (0.7)	23 (1.1) (1.0)	0.001
Central venous catheter-related bloodstream infection	12 (1.1) (4.1)	25 (1.8) (4.2)	102 (4.8) (7.2)	0.001
Infection-relationship mortality rates	77 (7.3) (12.5)	67 (5.0) (6.4)	80 (3.8) (3.5)	0.0001
<i>Acinetobacter baumannii</i> infections	42 (3.9) (6.8)	17 (1.2) (1.6)	38 (1.8) (1.6)	0.0001
<i>Klebsiella pneumoniae</i> infections	19 (1.8) (3.0)	10 (0.7) (9.5)	46 (2.2) (2.0)	0.005
<i>Pseudomonas aeruginosa</i> infections	21 (2.0) (3.4)	15 (1.1) (1.4)	19 (0.9) (0.8)	0.032
<i>Candida</i> spp. infections	3 (0.3) (0.1)	7 (0.5) (0.6)	38 (1.8) (1.6)	0.001
<i>Escherichia coli</i> infections	9 (0.9) (1.4)	7 (0.5) (0.6)	7 (0.3) (0.3)	0.159
<i>Enterobacter</i> spp. infections	5 (0.5) (0.8)	9 (0.7) (0.8)	5 (0.2) (0.2)	0.151
<i>Enterococcus</i> spp. infections	9 (0.9) (1.4)	3 (0.2) (0.2)	12 (0.6) (0.5)	0.110
Vancomycin resistant <i>Enterococcus</i> spp. infections	2 (0.1) (0.1)	0 (0.0) (0.0)	2 (0.09) (0.08)	0.304
Coagulase negative staphylococcus infections	5 (0.5) (0.1)	7 (0.5) (0.6)	3 (0.1) (0.1)	0.112
<i>Serratia marcescens</i> infections	0 (0.0) (0.0)	3 (0.2) (0.2)	3 (0.1) (0.1)	0.321
<i>Staphylococcus aureus</i> infections	4 (0.4) (0.1)	7 (0.5) (0.6)	2 (0.1) (0.1)	0.061
Methicillin-resistant <i>Staphylococcus aureus</i> infections	4 (0.4) (0.6)	5 (0.3) (0.4)	0 (0.0) (0.0)	0.019
<i>Stenotrophomonas maltophilia</i> infections	0 (0.0) (0.0)	1 (0.1) (0.1)	1 (0.0) (0.0)	0.685
<i>Proteus</i> spp. infections	1 (0.1) (0.1)	1 (0.1) (0.1)	5 (0.2) (0.2)	0.421
<i>Citrobacter</i> spp. infections	1 (0.1) (0.1)	0 (0.0) (0.0)	1 (0.0) (0.0)	0.552
Other streptococcus infections	0 (0.0) (0.0)	1 (0.1) (0.1)	0 (0.0) (0.0)	0.305

during SP-2, not only G2C consumption but also total antibiotic consumption decreased. We think that these findings are important for the rational use of antibiotics. With the spread of this application, restriction of some antibiotics might be implemented in antibiotic stewardship programs (16).

We also examined total mortality, frequency of *Acinetobacter* infections, and mortality from infections other than *Acinetobacter* during restricted and unrestricted periods. We found that mortality due to *Acinetobacter* or non-*Acinetobacter* infections did not increase.

An important result of our study is that ICU pseudomonas epidemiology is clearly influenced by antibiotic consumption. Our results suggest that if wide spectrum antibiotic consumption can be limited, pseudomonas infection rate will decrease. On the other

hand, we observed that *Candida* spp.-related infections tended to increase in spite of decrease in antibiotic consumption. We do not have a significant hypothesis about this finding. It needs a more comprehensive investigation.

The most important limitation of our work is that the study design was performed retrospectively and in a single center. If this work could be done as a multicenter study, local differences such as training frequency, infection control practices, and acceptance of new knowledge by some physicians could be excluded.

Finally, hospitals should monitor antibiotic use policies during certain periods and develop restricted formulas based on their own observations. As a result, we think that well-planned antibiotic restraint practices can play an important role in encouraging rational antibiotic use.

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