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BRIEF REPORT – OPEN ACCESS

The Effect of Carbapenem Restriction Policy on the Rate of Hospital Infections Due To Resistant Microorganisms in the Intensive Care Unit

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ABSTRACT

This study aims to investigate the effect of carbapenem restriction on the infection rate and antibiotic susceptibility. We divided the study period into two: carbapenem-free period (CFP) and carbapenem-restricted period (CRP). We compared the usage rate of antipseudomonal carbapenem, the incidence of nosocomial infection, invasive device days, the causative microorganisms, and antibiotic susceptibility. The nosocomial infection density was 40.95±19.02 in 1000 patient days in the CFP, and 20.71±4.28 in 1000 patient days in the CRP. We observed no significant difference between the two periods in terms of invasive devices use rates. Anti pseudomonal carbapenem usage rate was 2.73 in CFP and 1.67 in CRP. Of the 40 nosocomial infections due to *Acinetobacter baumannii*, 27 of them were found in the CFP. Carbapenem restriction policy may contribute to decrease the rate of resistant bacterial infections.

Keywords: *Acinetobacter baumannii* carbapenem, carbapenem restriction, defined daily dose, hospital infection

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INTRODUCTION

Nosocomial infections due to resistant gram-negative bacteria have become a major problem in the intensive care units (ICU) worldwide. These infections may result in the development of treatment difficulties of patients, prolonged intensive care stay, increased morbidity, mortality, and treatment cost (1). The most common difficulty for the treatment of resistant microorganisms is the inability to receive appropriate antibiotic therapy (2).

In recent years, high carbapenem-resistance rate has brought the using of alternative treatments especially in the ICUs. One of the alternative antibiotics is colistin. After the colistin treatment, side effects such as nephrotoxicity and neurotoxicity are major problems (3). The rate of colistin-associated nephrotoxicity varies between 20% and 30%, and nephrotoxicity has been reported to be associated with particularly high dose and long-term administration (4). The appropriate dose of colistin for effective tissue concentration is still unknown; and the onset of colistin-resistant strains indicates that this treatment is no longer sufficient (3). In recent years, the number of antibacterial approved by the FDA is very low, and these antibacterial drugs are not sufficient for the treatment of carbapenem and colistin-resistant strains (5).

This study is aimed to evaluate changes in the prevalence of infections caused by multidrug-resistant microorganisms with the restriction of the use of carbapenem.

MATERIALS and METHODS

Study Design

This study was conducted in a 1500-bed tertiary-care hospital in Anatolian region. We evaluated the medical records of patients who were hospitalized in the anesthesia and reanimation intensive care unit in University of Health Science, Kayseri Training and Research Hospital from January 01, 2017, to December 31, 2017. The local ethics committee approved the study with the number of 11-2018 on the date of 11.01.2018.

We divided the study period into two: carbapenem-free period (CFP) and carbapenem-restricted period (CRP).

During CFP, carbapenem used without any restriction in conditions was deemed appropriate. The carbapenem usage was restricted during CRP in the presence of an alternative therapy. Alternative options other than carbapenem were preferred. During the CRP, other options including piperacillin-tazobactam, cefoperazone-sulbactam, cefepime, tigecycline, ciprofloxacin, and colistin were allowed. No restriction was allowed if the strain was sensitive only to carbapenems. The use of antipseudomonal carbapenem, the incidence of nosocomial infection and invasive device days, and the incidence of the causative microorganisms in nosocomial infections were compared in both periods.

Table 1. Comparison of patient numbers, invasive device days, nosocomial infection densities, cumulative values of defined daily doses of antibiotics, number of infections due to microorganisms, and resistance rates in both periods

	Carbapenem free	Carbapenem restricted	p
Number of the patients (n)	485	647	
Age median (min–max)	55 (65–75)	61 (46–76)	0.48
Female gender (%), median (min–max)	55 (40–85)	78 (40–100)	0.24
Ventilator usage rate (100 patient days) median (min–max)	0.37 (0.18–0.47)	0.30 (0.10–0.43)	0.31
Central catheter utilization rate (100 patient days) median (min–max)	0.38 (0.20–0.80)	0.32 (0.25–0.70)	0.81
Urinary catheter utilization rate (100 patient days) median (min–max)	0.93 (0.87–1)	0.91 (0.87–1)	0.69
Nosocomial infection density (100 patient days) mean±SD	40.95±19.02	20.71±4.28	**0.029**
Meropenem*	2.73	1.67	**0.005**
Ertapenem*	0.053	0.075	0.196
Ciprofloxacin*	0.127	0.263	0.095
Amikacin*	0.082	0.062	0.744
Piperacillin-Tazobactam*	0.014	0.018	0.219
A. baumanii	27	13	**0.032**
Carbapenem resistance n (%)	13 (48%)	6 (46%)	
P. aeruginosa	17	6	0.147
Carbapenem resistance n (%)	10 (58%)	0 (0%)	
K. pneumoniae	18	18	0.155
Carbapenem resistance n (%)	4 (22%)	14 (77%)	
E. coli	4	1	0.209
Candida spp.	7	1	**0.022**

*Cumulative values of defined daily doses of 100 patient days

Study Population

In both periods, patients who were followed up in intensive care unit and diagnosed with nosocomial infection by the Infection Control Committee were included in the study.

Inclusion Criteria

1. Patients with pneumonia, catheter-related bloodstream infection, urinary system infection, and surgical site infection according to Centers for Disease Control and Prevention (CDC) diagnostic criteria (6).
2. Patients who received at least 72 h of carbapenem and other antibiotic treatment.

Exclusion Criteria

1. Patients with missing data
2. <18 years of age
3. Pregnancy

Amount of Antimicrobial Drugs

The study calculated the amount of drugs in the form of prescribed dose per 1000 bed days (defined daily doses (DDD)/1000 bed days). The antibiotic usage rate was compared in both periods, and the formula of the average daily volume of drug use in the indications for adult patients without indicating the correct dose of the treatment was used (7).

DDD (g) /1000-day bed=(amount of drug used in unit grams)×1000

DDD*×number of day beds

The World Health Organization defined DDD for each drug: meropenem: 2 g; imipenem: 2 g; ertapenem: 1 g; piperacillin-tazobactam: 14 g; ciprofloxacin: 0.5 g; amikacin: 1 g (8).

Statistical Methods

Statistical analyses were performed using SPSS version 21. Comparison of appropriateness between prescribing before and after using the antimicrobial restriction system was performed using Fisher's exact test and Pearson chi-square test. All test results of statistical significance were two-sided, with the significance level set at 0.05.

RESULTS

A total of 1132 patients, including 485 in the carbapenem-free period and 647 in the carbapenem-restricted period, were followed. Nosocomial infection density was 40.95±19.02 in 1000 patient days in the carbapenem-free period, and 20.71±4.28 in 1000 patient days in the restricted period (p=0.029). The median age was 55 years in CFP and 61 years in CRP. The ratio of female gender was 55% in CFP and 78% in CRP. The median ventilator usage rate in 100 patient days was 0.37 in CFP and 0.30 in CRP. The median central catheter utilization rate in 100 patient days was 0.38 in CFP and 0.32 in CRP. The median urinary catheter utilization rate 100 patient days was 0.93 in CFP and 0.91 in CRP (Table 1). Antipseudomonal carbapenem usage rate was 2.73 in DDD/1000 bed days cumulative dose of CFP, and it decreased to 1.67 in CRP (p=0.005). On the other hand, the usage rate

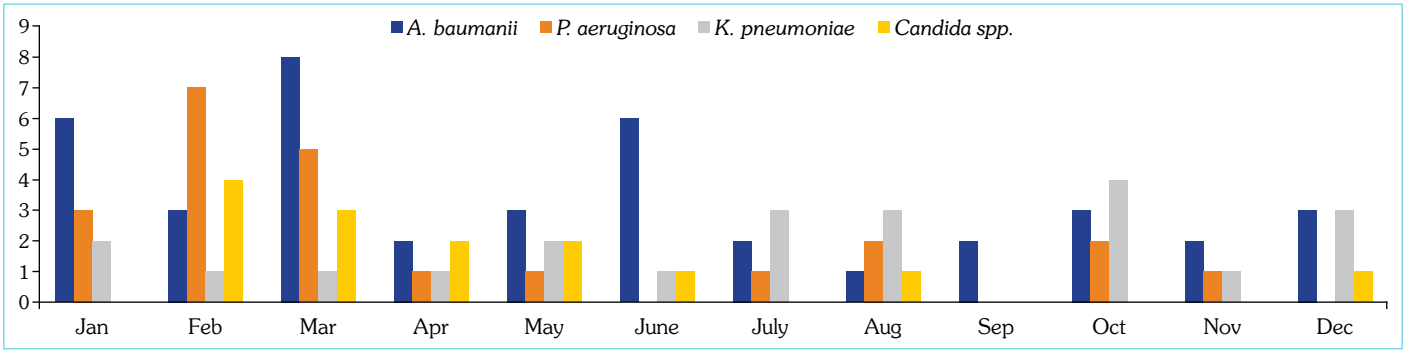

Figure 1. Distribution of nosocomial infection agents according to months

of ciprofloxacin DDD/1000 bed days increased from 0.127 to 0.263, and the usage rate of ertapenem increased from 0.053 to 0.075. We observed no difference in use of piperacillin-tazobactam and amikacin (Table 1). Of the 40 nosocomial infections due to *A. baumannii*, 27 were found in the CFP and 13 were found in the CRP. Carbapenem-resistance rate for *A. baumannii* was 48% and 46% respectively. There were 17 Pseudomonas spp. infections in the CFP and 6 Pseudomonas spp. infections in the CRP. There was no carbapenem resistance of Pseudomonas spp. in the CRP, but the carbapenem-resistance rate was 41% in the CFP. Eighteen *K. pneumoniae* infections were seen in the both CFP and CRP. However, the rate of carbapenem-resistance rate was 22% during the CFP and 77% during the CRP. Nosocomial infection number due to candidiasis were seven in the CFP and one in the CRP (p=0.022). A reduction in the number of nosocomial infections was seen due to *E. coli* in CRP (Table 1, Figure 1).

DISCUSSION

In this study, nosocomial infections due to MDR microorganisms decreased as 1.9-fold after the carbapenem restriction. A decrease has been shown in nosocomial infections due to resistant microorganisms after antibiotic restriction in antibiotic stewardship programs (9). Following the national antibiotic restriction program, carbapenem using has been reduced in the five tertiary health care centers, and the number of carbapenem-resistant *A. baumannii* and *P. aeruginosa* isolates has decreased. When the cost effectiveness is evaluated after this program, a gain of over five million dollars has been achieved (10). In this study, we observed no difference between the two periods in terms of factors such as age, gender, or invasive device usage rates that would affect nosocomial infection rate.

The reduction in antipseudomonal carbapenem usage has led to an increase in the use of quinolones and ertapenem in the second period. Increases in the use of ertapenem and aminoglycoside have similarly been reported in studies that have been restricted in the use of antipseudomonal carbapenems (9). In another study that applied carbapenem restriction, an increase in the use of piperacillin-tazobactam and cefepime was reported (10). In the study of Wu et al. (11) the use of second-generation cephalosporin and aminoglycoside decreased together with carbapenems. When we compare our results with literature, we have seen that changes of antibiotic using other than carbapenems may change with each patient's condition and antimicrobial resistance profile.

Compared with the two study periods, there was a marked decrease in the number of nosocomial infections due to *A. baumannii* and *P. aeruginosa*. Öğütlü et al. (9) reported a 2.24-fold decrease the number of nosocomial infections due to *A. baumannii* and 2-fold decrease due to *P. aeruginosa* after a carbapenem restriction study. When we compared the resistance rates, only carbapenem resistance was reduced in *Pseudomonas* strains. In a study evaluating the results of a three-year carbapenem restriction application, all gram-negative bacteria showed a decrease in carbapenem resistance within three years and carbapenem resistance decreased from 74% to 52.5% in *A. baumannii* (11). To compare antibacterial susceptibility when evaluated by the results of studies in the literature seems to require a longer than six months of carbapenem restriction.

When we compared the number of candidiasis in both periods, there was a marked reduction in carbapenem-restricted period. One of the risk factors for invasive candida infections is the use of broad-spectrum antibiotics (12). The reduction of the use of broad-spectrum antibiotics such as carbapenems can also be effective in the formation of collateral damages such as fungemia other than resistant bacterial infections.

As a conclusion, application of carbapenem restriction in intensive care units may contribute to decrease of collateral damage such as resistance to bacteria, decrease of gram-negative bacterial infection rates, and fungemia. However, we could not evaluate the change in resistance rates because the duration of the periods compared to the study was short. Studies of longer duration are needed to determine the effect of the carbapenem restriction policy on antibiotic susceptibility.

Ethics Committee Approval: The local ethics committee approved the study with the number of 11-2018 on the date of 11.01.2018.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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