Positive effect of restrictions on antibiotic consumption

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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...
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,
vancocin, teicoplanin, daptomycin, linezolid,
colistin, piperacillin/tazobactam, sulbactam, cepfime,
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
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 eritapenem 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,
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.

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

<table>
<thead>
<tr>
<th>Explanation</th>
<th>Study period 1 n (%) (density ‰)</th>
<th>Study period 2 n (%) (density ‰)</th>
<th>Study period 3 n (%) (density ‰)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>1053 (11.4) (19.6)</td>
<td>1322 (11.4) (19.6)</td>
<td>2085 (11.4) (19.6)</td>
<td></td>
</tr>
<tr>
<td>Patient days (n)</td>
<td>6143 (11.4) (19.6)</td>
<td>10444 (11.4) (19.6)</td>
<td>22827 (11.4) (19.6)</td>
<td></td>
</tr>
<tr>
<td>Hospital infections (n)</td>
<td>121 (6.0) (7.6)</td>
<td>80 (6.0) (7.6)</td>
<td>164 (7.8) (7.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>56 (3.2) (6.1)</td>
<td>32 (2.4) (6.1)</td>
<td>13 (0.6) (1.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinary catheter-related urinary tract infection</td>
<td>23 (4.0) (6.1)</td>
<td>7 (0.5) (0.7)</td>
<td>23 (1.1) (1.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Central venous catheter-related bloodstream infection</td>
<td>12 (4.1) (6.1)</td>
<td>25 (1.8) (6.2)</td>
<td>102 (4.8) (7.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Infection-relationship mortality rates</td>
<td>77 (7.3) (12.5)</td>
<td>67 (5.0) (6.4)</td>
<td>80 (3.8) (3.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em> infections</td>
<td>42 (6.8) (11.4)</td>
<td>17 (1.2) (1.6)</td>
<td>38 (1.8) (1.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> infections</td>
<td>19 (3.0) (12.5)</td>
<td>10 (0.7) (0.9)</td>
<td>46 (2.2) (2.0)</td>
<td>0.005</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> infections</td>
<td>21 (3.4) (12.5)</td>
<td>15 (1.1) (1.4)</td>
<td>19 (0.9) (0.8)</td>
<td>0.032</td>
</tr>
<tr>
<td><em>Candida</em> spp. infections</td>
<td>3 (0.1) (0.1)</td>
<td>7 (0.5) (0.6)</td>
<td>38 (1.8) (1.6)</td>
<td>0.001</td>
</tr>
<tr>
<td><em>Escherichia coli</em> infections</td>
<td>9 (1.4) (4.1)</td>
<td>7 (0.5) (0.6)</td>
<td>7 (0.3) (0.3)</td>
<td>0.159</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp. infections</td>
<td>5 (0.8) (0.8)</td>
<td>9 (0.7) (0.8)</td>
<td>5 (0.2) (0.2)</td>
<td>0.151</td>
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<tr>
<td><em>Enterococcus</em> spp. infections</td>
<td>9 (1.4) (4.1)</td>
<td>3 (0.2) (0.2)</td>
<td>12 (0.6) (0.5)</td>
<td>0.110</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus</em> spp. infections</td>
<td>2 (0.1) (0.1)</td>
<td>0 (0.0) (0.0)</td>
<td>2 (0.09) (0.08)</td>
<td>0.304</td>
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<tr>
<td>Coagulase negative staphylococcus infections</td>
<td>5 (0.1) (0.1)</td>
<td>7 (0.5) (0.6)</td>
<td>3 (0.1) (0.1)</td>
<td>0.122</td>
</tr>
<tr>
<td><em>Serratia marcescens</em> infections</td>
<td>0 (0.0) (0.0)</td>
<td>3 (0.2) (0.2)</td>
<td>3 (0.1) (0.1)</td>
<td>0.321</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> infections</td>
<td>4 (0.1) (0.1)</td>
<td>7 (0.5) (0.6)</td>
<td>2 (0.1) (0.1)</td>
<td>0.061</td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> infections</td>
<td>4 (0.6) (0.6)</td>
<td>5 (0.3) (0.4)</td>
<td>0 (0.0) (0.0)</td>
<td>0.019</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em> infections</td>
<td>0 (0.0) (0.0)</td>
<td>1 (0.1) (0.1)</td>
<td>1 (0.0) (0.0)</td>
<td>0.685</td>
</tr>
<tr>
<td><em>Proteus</em> spp. infections</td>
<td>1 (0.1) (0.1)</td>
<td>1 (0.1) (0.1)</td>
<td>5 (0.2) (0.2)</td>
<td>0.421</td>
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<td><em>Citrobacter</em> spp. infections</td>
<td>1 (0.1) (0.1)</td>
<td>0 (0.0) (0.0)</td>
<td>1 (0.0) (0.0)</td>
<td>0.552</td>
</tr>
<tr>
<td>Other streptococcus infections</td>
<td>0 (0.0) (0.0)</td>
<td>1 (0.1) (0.1)</td>
<td>0 (0.0) (0.0)</td>
<td>0.305</td>
</tr>
</tbody>
</table>
References


